ASYMMETRIC HYDROGENATION OVER SUPPORTED NICKEL CATALYSTS

BY

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To my mum and dad

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SUMMARY

The use of Ni/SiO_2 catalysts modified in aqueous solutions of optically pure (R,R) tartaric acid for the asymmetric hydrogenation of methyl acetoacetate to methyl 3-hydroxybutanoate has been studied in detail.

This study into the effect of the modification variables, namely tartaric acid concentration, temperature and pH on the enantiodifferentiating ability of Ni/SiO_2 catalysts, has shown that each of these variables exert an influence on the extent of nickel corrosion during modification as well as the enantiodifferentiating ability of the resultant catalyst. In contrast to previous reports in the literature, aimed at a specification of standard conditions for nickel catalyst modification, this study has shown that, due to the corrosive nature of modification, highest values for enantioselectivity are achieved when specific conditions are derived for the individual catalyst.

Ni/SiO_2 catalysts of higher nickel loading are more resistant to the inherent corrosiveness of the tartaric acid modification procedure and, in consequence, are capable of exhibiting greater enantiodifferentiating ability than catalysts which have low nickel loading. The adsorption of tartaric acid results in the formation of a nickel/tartaric acid surface complex, a quantity of which can be degraded to a nickel (II) tartrate complex

which is washed into solution.

From the results of this study a mechanism for the enantioselective and racemic hydrogenation of methyl acetoacetate to methyl 3-hydroxybutanoate is suggested. It is proposed that a nickel/tartaric acid complex is formed on the surface during modification and that this complex controls the stereochemistry of the adsorbed substrate which is hydrogenated. Bare nickel sites are still present on the catalyst surface after modification and these are considered to be responsible for hydrogen activation and for racemic hydrogenation. It is also proposed that spill-over of hydrogen from the bare nickel sites to the nickel/tartaric acid/adsorbed methyl acetoacetate complex is a prerequisite for enantioselective hydrogenation.

The enhancement in enantioselectivity when sodium bromide is used as a co-modifier has been demonstrated to be the result of a partial poisoning of non-selective sites remaining on the catalyst surface after modification.

CHAPTER ONE

INTRODUCTION

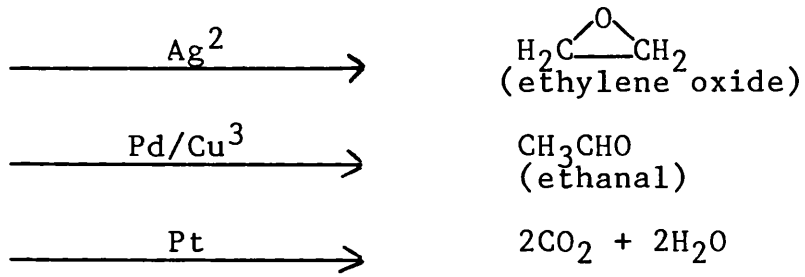
Section 1.1 Catalyst Selectivity.

The selectivity of a catalyst to preferentially catalyse one of several thermodynamically possible reactions is an important feature of heterogeneous catalysis. The importance and the scope of selectivity in heterogeneous systems are described in "The Second Rideal Lecture; What makes a catalyst selective?" by Sachtler[1].

The diversity in the area of, and reason for catalyst selectivity is illustrated by the following examples:-

1 Product Selectivity. In the catalytic oxidation of ethene(C_2H_4), the products of oxidation vary with the metal component of the catalyst.(Figure 1.1a)

Figure 1.1a

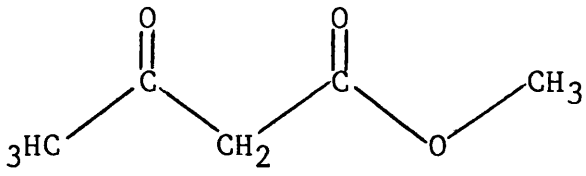


2 Stereoselectivity (the preference for one configurational isomer [e.g.enantiomer] over the other). The stereochemistry of ligands attached to a catalytic site act as 'templates' controlling the stereoselectivity of product formation.

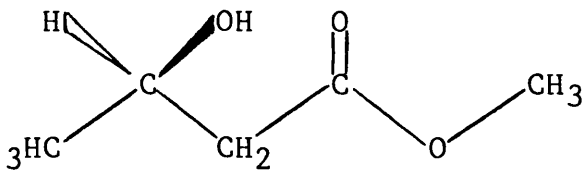
This thesis is concerned with the type of selectivity

mentioned in (2) above. In particular, the use of nickel catalysts 'modified' by optically pure tartaric acid and used in the 'enantioselective' hydrogenation of methyl acetoacetate (MAA) [Figure 1.1.1a] to methyl 3-hydroxy butanoate (MHB) [Figure 1.1.1b].

Figure 1.1.1



(a)
Methyl Acetoacetate (MAA).



(b)
Methyl 3-Hydroxy Butanoate (MHB).

Figure 1.1.1b is the 'R' enantiomer of MHB.

In this chapter the discovery and development of Ni catalysts which exhibit this type of selectivity are described, preceded by a description of relevant organic stereochemistry and nomenclature (which explains the ' ' highlighted terms in this section),asymmetric synthesis, and homogeneous asymmetric catalysis.

Section 1.2 Organic Stereochemistry, Nomenclature And Syntheses.

Section 1.2.1

Stereoisomers.

Stereochemistry is chemistry in three dimensional space. For example, by considering the orientation of the atoms of two separate molecules in space, a difference may be noted which is not reflected in their identical condensed structural formula. These two molecules are therefore 'stereoisomers', and can be classified as either conformational isomers (rotation around a C-C single bond of one isomer would give the other, a process that occurs rapidly at room temperature) or configurational isomers, where intercoversion of isomers is not possible by a simple rotation around bonds of the molecules.

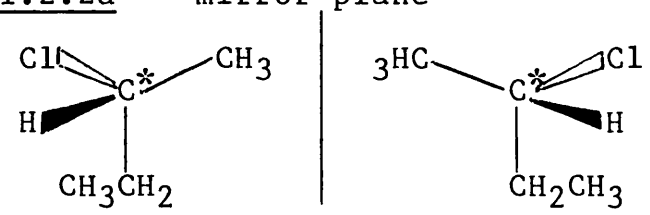
Thus in catalytic procedures, stereoselectivity is the preferential production of a particular configurational isomer.

Section 1.2.2

Configurational Isomers And Chirality.

Configurational isomers can be assigned as enantiomers or diastereomers[4]. Enantiomers are stereoisomers that are mirror images of each other. All configurational isomers that are not enantiomers are diastereomers. An example of an enantiomer pair is shown in Figure 1.2.2a.

Figure 1.2.2a



[a] (-) 2 Chlorobutane [b] (+) 2 Chlorobutane
[a] is non-superimposable on [b].

The second carbon (*)of 2 Chlorobutane is a Stereogenic centre as this carbon is bonded to four different groups. As [a] is non-superimposable on [b], its mirror image, the molecule is said to be chiral[5]. In this example the presence of the stereogenic centre induces chirality, though the primary criterion for chirality is that a molecule is non-superimposable on its mirror image[6]. Diastereomers can be superimposed on their mirror image and are termed achiral.

Enantiomers have identical physical properties (such as boiling point) with one exception- they rotate plane polarised light in opposite directions. In Figure 1.2.2 a the name of enantiomer [a] is preceded by a (-) sign, indicative that this enantiomer rotates plane polarised light counter-clockwise. The enantiomer [b] rotates plane polarised light clockwise and is denoted by the (+) sign. Each enantiomer rotates plane polarised light to the same extent in opposite directions. Thus enantiomers are said to be optically active, and a pure sample of an enantiomer is said to be optically pure.

Diastereomers do not rotate plane polarised light.

While (+) and (-) preceding enantiomeric names indicate the direction of optical acivity, they give no indication as to the actual configuration of each enantiomer. The system used to distinguish one enantiomer from the other, by using a naming system which gives the configuration of each enantiomer, is described fully in the next Section.

Section 1.2.3 The Cahn-Ingold-Prelog Rules.

The system which defines the configuration at a stereogenic centre was created by Cahn-Ingold-Prelog[7] and is summarised as follows:-

1./ Each of the four non-identical groups attached to the tetrahedral carbon (the stereogenic centre) is assigned a priority. The higher the atomic number of the atom bonded directly to the stereogenic centre, the higher the priority of the substituent, for example-

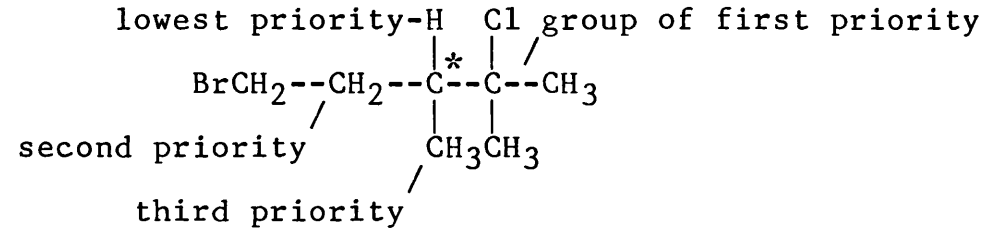
Cl > O > N > C > H

In the case of isotopes, the highest atomic weight takes priority, for example the isotopes of hydrogen-

T > D > H

2./ If two identical atoms are attached to the stereo-genic centre, the next atoms in both chains are investigated, moving away from the stereogenic centre

until some difference is found. A priority assignment is made at the first point at which atoms of different priorities are found. e.g.



C* is the stereogenic centre.

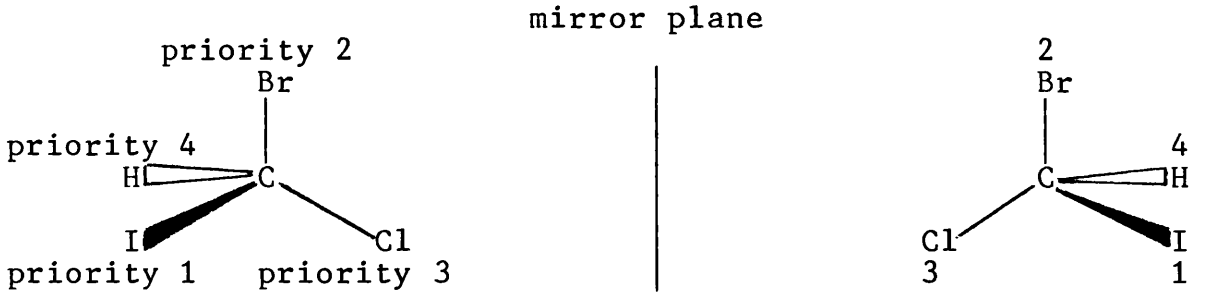
Although the group of second priority has a Br atom at the end of the chain, it does not influence the assignment of priorities because it is beyond the point of difference.

3./ A double bond is counted as two single bonds for both of the atoms involved;

The same principle is extended to triple bonds.

4./ After priorities have been assigned, the molecule is viewed with the substituent of lowest priority away from the viewer. If the path taken by following group priorities in order (1^{st} to 3^{rd}) is clockwise, the stereogenic centre is assigned the R (rectus) configuration. If priorities follow a counterclockwise path, the configuration is S (sinister).

For example:-



clockwise counterclockwise

(R) bromochloroiodomethane (S) bromochloroiodomethane

5./ For molecules with more than one stereogenic centre, each centre is assigned its own configuration

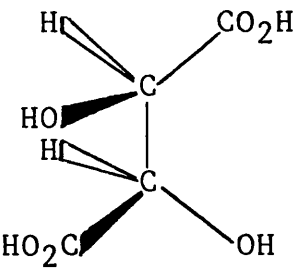
It is a matter of convention that when naming enantiomers using the Cahn-Ingold-Prelog rules to include the sign (+ or-) relating to the direction of rotation of plane polarised light.

Section 1.2.4 Compounds With More Than One Stereogenic Centre.

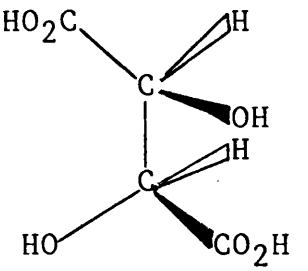
Organic molecules that have n stereogenic centres will have a maximum number of 2^n stereoisomers[8]. For example, tartaric acid has 2 stereogenic centres and therefore a possible maximum of 4 configurational isomers. These are shown in Figure 1.2.4a.

Figure 1.2.4a

mirror plane

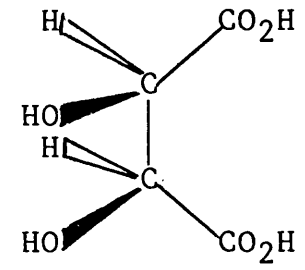


(2R,3R)-[+]-tartaric acid
I

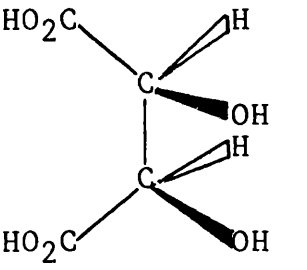


(2S,3S)-[-]-tartaric acid
II

mirror plane



(2R,3S) tartaric acid
III



(2S,3R) tartaric acid
IV

On inspection, I & II are an enantiomer pair but III is superimposable on its mirror image IV i.e. III & IV are diastereomers. This is due to the fact that although there are two stereogenic centres, the substituents of each are the same, giving a plane of symmetry that bisects the C^2--C^3 bond of III (or IV). Thus III is achiral and has no optical activity, and is called the meso form of tartaric acid. This example illustrates why the primary criterion for chirality, which is that a molecule cannot be superimposed on its mirror image and

not the presence of stereogenic centres.

Section 1.2.5 Plane Polarised Light.

In Section 1.2.2, it was stated that the only difference in the physical properties of an enantiomer pair is that each rotated the plane polarised light by the same amount in opposite directions. Brief descriptions of plane polarised light[9,10] (1) and why chiral molecules rotate the plane of polarisation (2) are as follows:-

(1) Light is generally characterised as a wave with associated oscillating electric and magnetic fields. Thus for a beam of light, one vector describes the electric field strength, and another the magnetic field strength. These vectors are in planes that are perpendicular to each other and the direction of the propagation of the wave. In ordinary light, there are a great number of these electromagnetic waves, the vectors of each wave have a random orientation with respect to those of other waves. Certain crystalline substances e.g. calcite, only allow the passage of light waves with their electric vectors in one plane, thus transmitting light that is said to be plane polarised.

(2)The interaction of plane polarised light with molecules changes the direction of the plane of

polarisation. If the molecules are achiral, the interactions which take place do not result in an overall change in the plane of polarisation. This is because any 'twist' given to the plane by a molecule in a particular orientation, is cancelled by a 'twist' in the opposite direction caused by a molecule in another orientation that is the mirror image of the first one. If the molecules are chiral, no molecular orientation is the exact mirror image of any other. Therefore the changes in the plane of the polarisation are not cancelled out, but add up to give rotation of plane polarised light.

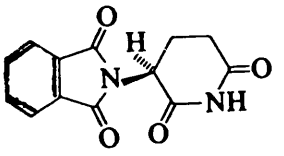
Experimentally, the measurement of the rotation of plane polarised light is termed Polarimetry.

Section 1.2.6 The Occurrence of Enantiomers in Nature.

Though the only difference in the physical properties of enantiomers is the rotation of plane polarised light, a more important difference is noted in the natural occurrence of enantiomers. Most naturally occurring compounds exist only as one of two possible enantiomers, for example carbohydrates and proteins in living organisms. Bioligical systems (such as enzymes[11]) can distinguish between one enantiomer and its mirror image. Thus, one enantiomer of a compound may be a hormone or

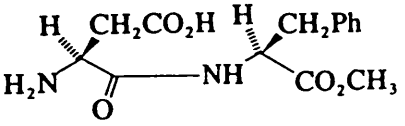
active as a medication, and the other enantiomer may be biologically inactive. More importantly, one enantiomer may be active, while the other has an undesired effect, for example, both enantiomers of thalidomide have the desired sedative activity, but the (S)-[-]-enantiomer (Figure 1.2.6a) has teratogenic properties[12] (i.e. foetal deformaties).

Figure 1.2.6a



Another example is the artificial sweetener (S,S) aspartame (Figure 1.2.6b), where the other three isomers (R,S;S,R;R,R) are bitter tasting[12].

Figure 1.2.6b



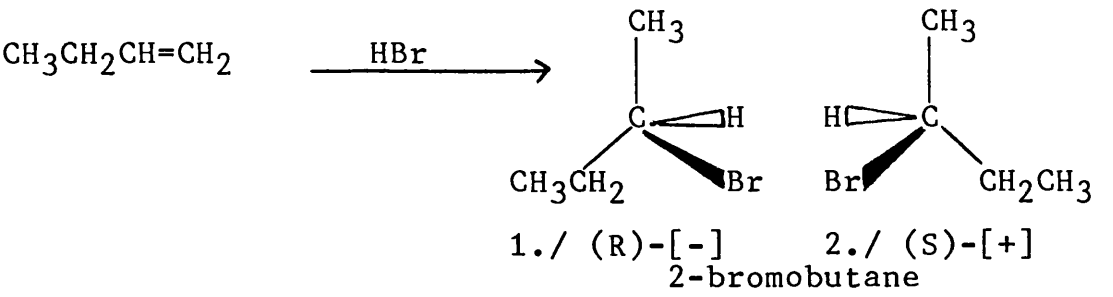
Therefore in the synthesis of enantiomers, it is often necessary that one enantiomer is exclusively produced.

Section 1.2.7 Non Selective Synthesis.

In synthetic processes that generate enantiomers as the products, the usual outcome is that typified by the nature of the addition reaction of HBr to alkenes[13];

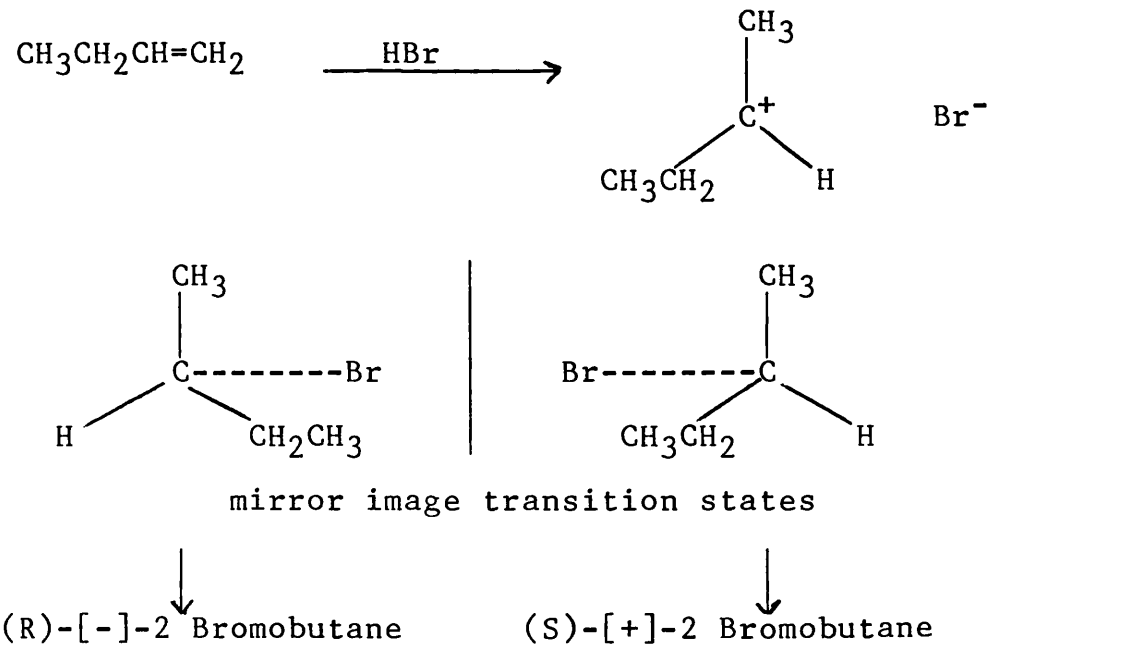
for example but-1-ene to 2-bromobutane (Figure 1.2.7a).

Figure 1.2.7a



An examination of the reaction mechanism shows that it should give an equal amount of each enantiomer, as the reaction proceeds via a planar carbocation[14,15] intermediate, a symmetrical achiral species. The bromide ion reacts with equal probability at either face of this cation as shown in Figure 1.2.7b.

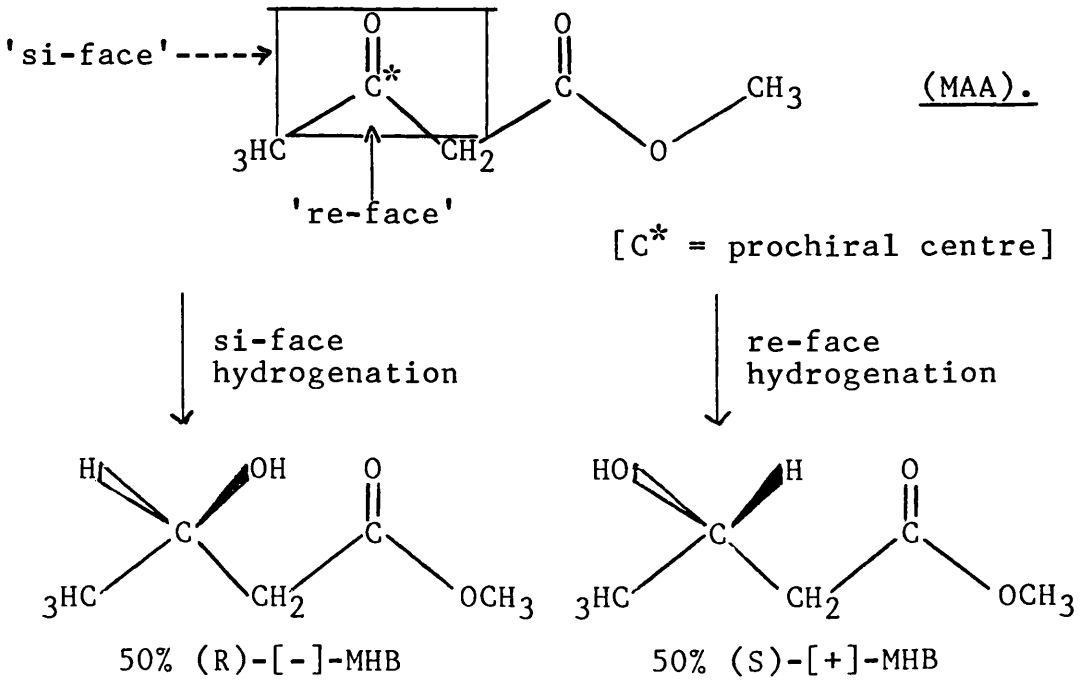
Figure 1.2.7b



The two possible transition states leading from the cation to the two different products are equal in energy. The two processes have the same energy of activation and consequently the same rate, so each enantiomer is formed in equal amounts. The product mixture is termed a Racemic mixture [i.e. a 50% (R): 50% (S) product mixture] and would exhibit no optical activity.

Analogous to this addition reaction (of HBr to the planar carbocation) is the reduction (hydrogenation) of carbonyl groups by an achiral reagent ($LiAlH_4$)[16] or by catalytic hydrogenation; there is equal probability of addition of hydrogen to either side of the plane e.g. the reduction of MAA to MHB [Section 1.1] :-

Figure 1.2.7c



50% (R)-[-]-MHB

50% (S)-[+]-MHB

In Figure 1.2.7c additional stereochemical nomenclature is included:- the carbon of the carbonyl group is prochiral because reduction of this group would create in equal quantaties, an enantiomer pair. Both faces of the plane which contains the carbonyl group are named using the Cahn-Ingold-Prelog rules - each group attached to the prochiral centre is given a priority, the face that has priorities decreasing in a clockwise direction is the re-face, the other is the si-face.

These two examples show why in non-selective syntheses, each enantiomer is formed with equal probability, and therefore in equal quantities.

Section 1.2.8 Asymmetric Synthesis/Catalysis.

In the previous section examples of non-selective syntheses were described, processes which give racemic mixtures of enantiomers that are inseparable by normal physical methods (e.g. fractional distillation). The need to produce for one enantiomer over the other, because of the differing biological activity [e.g. in pharmaceuticals, agrochemicals and food additives], (Section 1.2.6) has necessitated a requirement for the development of synthetic methods that are selective in the enantiomer they produce. Methods to achieve this goal are termed Stereoselective or more specifically

Enantioselective.

Inspection of the two examples of non-selective reactions in the previous section, shows that the preferential formation of one enantiomer over the other would involve the selective addition of the reagent [i.e. bromide or hydrogen] to one side of the plane of symmetry that contains the carbocation or prochiral carbonyl group so such processes are termed Asymmetric.

Thus, in this thesis, the catalytic hydrogenation of MAA to an excess of one enantiomer of MHB over the other is termed Asymmetric Hydrogenation Catalysis. Catalysts which are enantioselective in product formation are said to exhibit enantiodifferentiating ability.

The known methods of asymmetric synthesis have been classified into four different types[17] which are termed First, Second, Third and Fourth generation methods. The First to Third generation methods are an organic synthetic approach using chiral reagents or substrates, while the Fourth generation methods are catalyst controlled methods where the substrate and reagent are achiral and the catalyst is chiral. Fourth generation methods cover homogeneous, heterogeneous and enzyme catalysis. All the asymmetric synthetic methods have the basic underlying strategy of using enantiomerically pure naturally occuring compounds to influence the stereo-

chemical outcome of a reaction. The types of compounds that have been used are:-

i) amino acids and amino alcohols

ii) amines and alkaloids

iii) hydroxy acids (e.g. tartaric acid)

iv) terpenes (e.g. pinene, camphor)

v) carbohydrates

vi) enzymes and other proteins.

A few brief examples of their use are as follows:-

In heterogeneous asymmetric catalysis over nickel catalysts, compounds from groups i & iii [glutamic acid and tartaric acid][18] have been used in conjunction with the catalyst. Cinchonidene, a group ii compound, has been used with platinum catalysts in the asymmetric hydrogenation of ethyl pyruvate[19]. Compounds from the other groups have been used to form chiral reagents in organic synthesis e.g. diisopinocampheyl borane [a derivative of a group iv compound] reacts with alkenes to give an intermediate which is hydrolysed asymmetrically to give an excess of one alcohol over the other[20].

Section 1.2.9 Analysis of Product Mixtures From Asymmetric Synthesis.

The measure of success of an asymmetric synthetic

step is the enantiomeric excess (e.e.) produced. This is the difference in the concentration of each enantiomer divided by the sum of the concentration of each enantiomer expressed as a percentage:

$$\underset{\%}{e.e.} = \frac{C_R - C_S}{C_R + C_S} \times 100$$

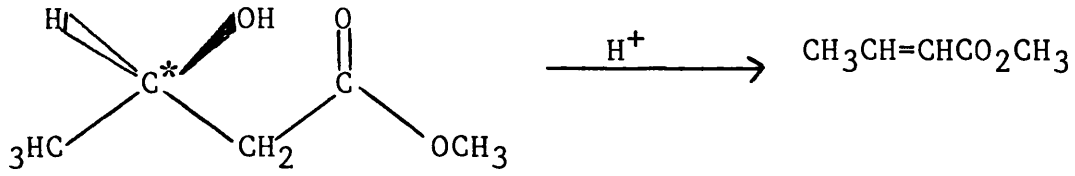
where C_R & C_S are the concentrations of each enantiomer Thus for a pure enantiomer e.e.= 100% and for a racemic mixture ($C_R = C_S$) e.e= 0%.

The enantiomeric excess can be calculated from chromatographic analysis and Polarimetric measurements, as used for analysis in this thesis (Section 3.4.3).

Alternate methods, for direct resolution, include chromatography (g.l.c. or h.p.l.c.) on a chiral stationary phase, n.m.r in the presence of a chiral lanthanide shift reagent(e.g. tris[3-heptafluoropropyl hydroxy methylene)-(+)-camphorato]-europium III[21]) or chiral solvent, but these methods are dependent on the commercial availability of suitable systems for the enantiomers of interest. For example the Pirkle type-1A 5μ reversible H.P.L.C. column separates chiral alcohols that have bulky substituents (such as phenyl-) attached to the stereogenic centre, but not the enantiomers of MHB. The literature supplied with the column suggested making derivatives of MHB with chiral acid chlorides,

but previous attempts to derivatise MHB had resulted in dehydration of the product, accompanied with loss of chirality (Figure 1.2.9a);

Figure 1.2.9a



The lack of success in derivatising MHB, and other methods of direct enantiomer resolution which were tried without success, are described elsewhere[22]. Generally, it is important that in the analysis of a product mixture after an asymmetric synthetic step the stereogenic centre is not destroyed.

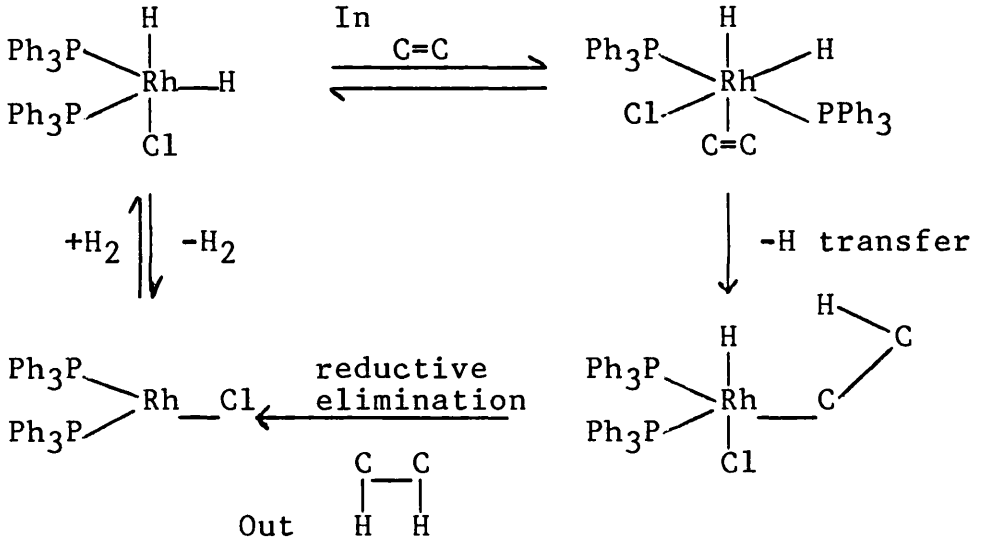
Section 1.3.1 Asymmetric Homogeneous Catalysis.

Though it was known for many years[23] that solutions of certain ions (Ag^+, MnO_4^-) had the ability to 'activate' molecular hydrogen, and the resultant species could be used to catalyse the slow reduction of unsaturated compounds, the first practical homogeneous catalyst for alkene and alkyne reduction under mild conditions was the complex $RhCl(PPh_3)_3$ named as Wilkinson's catalyst[24].

This complex works as a catalyst through the ability

to dissociate to a bisphosphine complex $RhCl(PPh_3)_2$, which is involved in the simplified catalytic cycle for alkenes shown in Figure 1.3.1a (the possible coordination of solvent molecules is ignored);

Figure 1.3.1a



Several features of the cycle satisfy the requirement for catalytic activity:-

1. The high lability of species that can exist in several forms because of dissociative equilibria e.g. $RhCl(PPh_3)_3 \rightleftharpoons RhCl(PPh_3)_2 + PPh_3$; $K=1.4\times10^{-4}M$
2. The changes in coordination numbers from 3 to 6 (or from 14- to 18- electron species).
3. The changes in the oxidation state from I to III in the oxidative-addition and reductive-elimination steps.

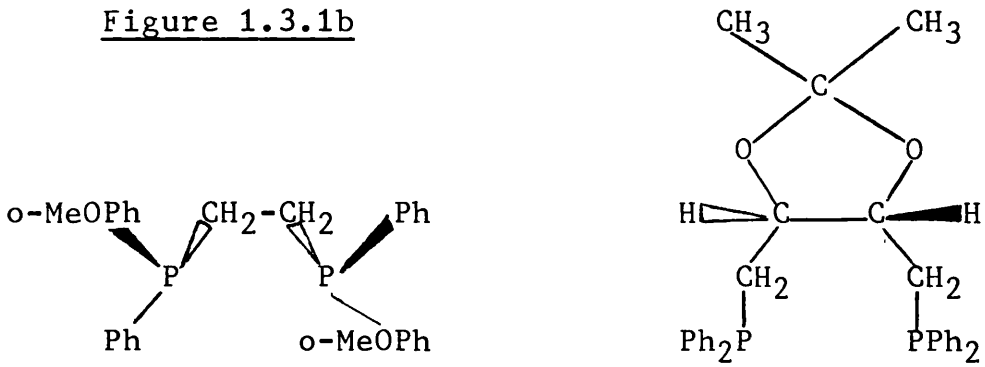
It is worth noting that in all catalytic cycles

involving tertiary phosphine complexes, the steric bulk of the ligands influence the dissociative equilibria as well as the orientation and complexing of the unsaturated substrate, and the stability of the intermediate alkyl.

From this basis, other tertiary phosphine complexes have been used as catalysts for the reduction of C=O, -N=N, -CH=N- and $-NO_2$ groups as well as alkenes and also alkynes[25]. The application has been broadened further still to asymmetric hydrogenation of prochiral substrates with complexes that have chiral tertiary phosphine ligands[26].

The chiral ligands used in the asymmetric homogeneous catalysts can be chiral through the configuration at the phosphorus atom, or at a carbon atom in a group attached to the phosphorus atom. An example of each is illustrated in Figure 1.3.1b.

Figure 1.3.1b



(a) (R,R)-DIPAMP (b) (R,R)-DIOP

[Ph-= Phenyl; o-MeOPh-= ortho methoxy Phenyl]

The names given to each ligand are abbreviations of

the full name, for example (R,R)-DIOP is (+)-2,3-O-dihydroxy-1,4-bis(diphenylphosphino)-butane, a derivative of tartaric acid[27].

While chiral rhodium complexes give high optical purity (ca. 95%) in the hydrogenation of prochiral olefins of the type $R'CH=C(NHR_2)COOH$[28] to chiral amino acids, the precise role of the chiral ligand is not fully understood. It is thought that the interactions between the coordinated prochiral substrate and either the metal or the phenyl rings lead to high asymmetric induction[29], due in the main to the stereoselectivity in the binding step rather than from the relative rates of formation or hydrogenation of the diastereomeric complexes.

Section 1.4 Asymmetric Heterogeneous Catalysis.

Section 1.4.1 Introduction.

The first reported example of heterogeneous catalysed asymmetric hydrogenation (which led to the development of enantioselective nickel catalysts) was that reported by Akabori concerning silk-Pd catalysts in 1956[30]. This type of catalyst was prepared by boiling silk fibroin (the water insoluable structural protein from silk) in an aqueous solution of a metal salt (in this case $PdCl_2$) followed by reduction under hydrogen gas. The basis for the study of this system was the belief that if a reaction was carried out on an achiral substrate in a chiral environment, an optically active product would be formed.

However, it was found that the enantiodifferentiating ability of the silk-Pd catalyst was low and irreproducible, and depended on the nature of the silk fibroin used. The study of these silk catalysts was continued by Izumi, who investigated the effect of altering the metal component (palladium,[31,32,33] platinum[34,35] and rhodium[36]) of the catalyst and found greater activity for the hydrogenation of $-NO_2$, C=N- and $\rangle C=C\langle$ groups than the unsupported metals, but poor hydrogenation activity for the carbonyl group of Methyl acetoacetate (MAA).

It was believed that the poor activity in carbonyl group hydrogenation was caused by an inhibition of the active site by the carbonyl groups of the protein (which have a stronger affinity for the active site). These are more resistant to hydrogenation so effectively block the active site, resulting in low levels of MAA hydrogenation. To discover if this was the case, a more conventional catalyst for carbonyl reduction (Raney nickel), was treated in protein solutions[37] but a loss of activity was observed. This was also the case for Raney nickel catalysts treated with aqueous solutions of various optically active amino and hydroxy acids; the treated catalysts were inactive for C=O hydrogenation at 283 K, but above 333 K a degree of an enantioselective hydrogenation reaction took place[38]. Izumi termed these catalysts as 'modified' rather than poisoned because of the positive effect in enantioselectivity, and the optically pure compounds used to treat the catalysts as 'modifying reagents'.

A more specific description of the first modified Raney nickel system is given after a description of the types of nickel catalyst that have been developed for asymmetric heterogeneous catalysis.

Section 1.4.2 Nickel Catalysts.

The phenomenon of asymmetric catalysis has been observed over three distinct types of nickel catalyst systems, namely-

i/ Raney nickel The study of asymmetric catalysis has concentrated on the use of Raney nickel and consequently the bulk of studies have centred on this type of catalyst. 'Raney catalyst' is the name given to all catalysts prepared by the method described by M. Raney[39] which involves the ingestion of one component from a binary alloy to leave a fine crystallite structure of the other metal. For example Raney nickel is prepared from a Ni:Al alloy, by ingesting the alloy in aqueous NaOH solution which leaches out the aluminium as sodium aluminate. The resultant Raney nickel is pyrophoric, and is a porous aggregate[40] (the average pore radius being 3.4 nm) of crystallites (diameter in the range 2.5 to 10 nm[40]). The Raney nickel catalyst is not pure nickel; there is some nickel oxide, hydrated alumina (1-20%) and aluminium (1-8%). Of the total metallic surface area (in the region of 50-130m^2g^{-1}), nickel accounts for 70-80% of this, the remainder comprised of surface aluminium in the catalyst[40,41].

ii/ Nickel powders. Some studies have used nickel

powders as catalysts, both for comparison with Raney nickel and because they are easier to handle than the pyrophoric Raney nickel[42]. The nickel powders used were either commercially available[42,43], were formed by the decomposition of highly pure nickel formate in vacuo followed by reduction in hydrogen[44] or by direct reduction of pure nickel oxide[45]. The variety in source of nickel powders used means that a general description characterising these catalysts cannot be given though individual studies have included information about powders used (e.g. T. Osawa[43] et al., used a commercially available Ni powder of mean particle diameter 20 nm).

iii/ Supported Nickel Catalysts. The third type of catalytic system used in asymmetric catalysis studies are supported nickel catalysts. These catalysts are prepared by dispersing a known quantity of a nickel salt on a support material (e.g. Al_2O_3[46] and SiO_2[47]), to form a catalyst precursor which is 'activated' prior to use i.e. the metal salt is reduced. Supported metal catalysts of various metal loadings (e.g. from 6[48] to 50[47] w/w% Ni loading) have been used as have different methods of catalyst precursor preparation (impregnation, precipitation[47]) Again there is no general description of these

catalysts, as each catalyst system is different because of differences in support, metal loading and catalyst precursor activation.

Throughout the rest of this chapter the catalyst is referred to by type only, unless some aspect of the unmodified catalyst is relevant to a particular point.

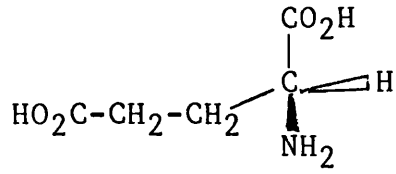
Section 1.4.3

The Development of Asymmetric Heterogeneous Catalysis Over Modified Nickel Catalysts. Initial Studies.

From the original report on asymmetric hydrogenation catalysis by Akabori[30] and the subsequent use of Raney nickel catalysts by Izumi et al.[37], the study of asymmetric heterogeneous catalysis has continued for over three decades. In this and following sections of this chapter the development of asymmetric catalysis is described, based on the available literature.

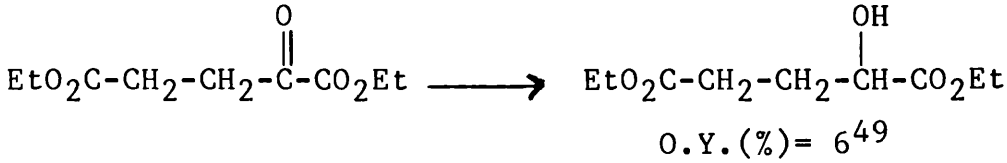
The initial studies by Izumi[38] referred to in Section 1.4.1 specifically concerned the asymmetric liquid phase hydrogenation of methyl acetoacetate (MAA, Figure 1.1.1) ,a β- ketoester, to methyl 3-hydroxybutanoate (MHB, Figure 1.1.1) over Raney nickel 'modified' in an aqueous solution of (S)-glutamic acid;

(S)-glutamic acid



The catalyst was modified in a solution of the optically active glutamic acid, the pH of which had been adjusted to 5.1, at a temperature of 273 K. The modified catalyst was then washed with distilled water and used to hydrogenate undiluted MAA at 333K. Analysis of the product mixture showed an optical yield [O.Y.(%)] of 15.3, with the (R) enantiomer of MHB in excess. It should be noted at this point that the optical yield is an alternate to the enantiomeric excess (Section 1.2.9) as a measure of the enantiodifferentiating ability of a catalyst and is also calculated from Polarimetry[47]. Independently, Isoda et al.[49], had also reported an enantioselective hydrogenation over Raney nickel catalysts treated with (S) glutamic acid; the hydrogenation of diethyl 2-oxoglutarate (Figure 1.4.3a) gave a product mixture that exhibited optical activity:-

Figure 1.4.3a



O.Y.(%)= 6[49]

These examples of asymmetric hydrogenation effected by a Raney nickel catalyst modified by a chiral reagent,

gave rise to the study of other amino and hydroxy acids as modifiers. The conclusions which could be drawn from the study of various chiral reagents as modifiers, in terms of the enantioselective activity (of MAA to MHB) of the resultant catalyst can be summarised as follows:-

1. Compounds of the general structure Rg-CHX-CO_2H (where X=NH_2 or OH) were found to be the most effective modifiers, inducing greater enantioselectivity to the Raney nickel than, for example, the corresponding alcohol (Rg-CHX-CHOH)[50]. The effect of a substituent on the C-2, N or O atom of the modifier was to decrease the optical yield, as shown in Table 1.4.3a-

Table 1.4.3a

Modifying Reagent	Modifying pH	$[\alpha]_D^{20}$*	O.Y.%
a[51]	5.1	-3.51	15.3
b[51]	5.55	-0.67	2.9
c[52]	6.1	-1.92	8.4
d[53]	5.0	-5.30	23.1
e[53]	5.2	-2.15	9.4

* The measured angle of rotation of plane polarised light by the product mixture.

The other conditions of modification and MAA reduction were the same as those for Raney nickel modified with (S) glutamic acid.

The modifying reagents (a to e) in Table 1.4.3a are as

follows:-

(a) (S)- $CO_2H-CH_2-CH_2-\underset{\displaystyle NH_2}{\underset{|}{CH}}-CO_2H$

(b) (S)- $CO_2H-CH_2-CH_2-\underset{\displaystyle NHCOC_6H_5}{\underset{|}{CH}}-CO_2H$

(c) (S)- $CO_2H-CH_2-CH_2-\underset{\displaystyle NH_2}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{CH}}}}-CO_2H$

(d) (R,R)- $CO_2H-\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle OH}{\underset{|}{CH}}-CO_2H$

(e) (R,R)- $CO_2H-\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle OCOC_6H_5}{\underset{|}{CH}}-CO_2H$

2. The configuration at the stereogenic centre of the modifying reagent was found to control the direction of enantioselectivity in the hydrogenation of MAA over modified catalysts: if a pure enantiomer used as a modifying reagent resulted in a catalyst that gave an excess of one enantiomer of MHB in the hydrogenation of MAA, the opposite enantiomer used as a modifying reagent would give an equal excess of the opposite enantiomer of MHB[38], for example-

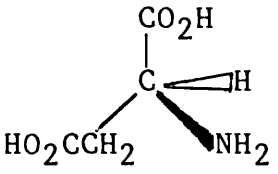
$$\text{MAA} \xrightarrow{\text{Raney nickel/ (R) glutamic acid}} \text{MHB O.Y.=+14\% excess(S) + MHB}$$

$$\text{MAA} \xrightarrow{\text{Raney nickel/ (S) glutamic acid}} \text{MHB O.Y.=-14\% excess(R) - MHB}$$

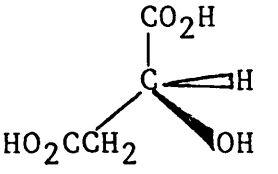
Another feature of the enantioselective behaviour of modified catalysts was that the same configuration at the stereogenic centre of amino and hydroxy acid modifiers (i.e. either R or S) resulted in catalysts that give opposite excesses of the enantiomers of MHB[56]:-

MAA $\xrightarrow{\text{Raney nickel/(S) aspartic acid}}$ excess (R) - MHB

$\xrightarrow{\text{Raney nickel/(S) malic acid}}$ excess (S) + MHB



(S) aspartic acid



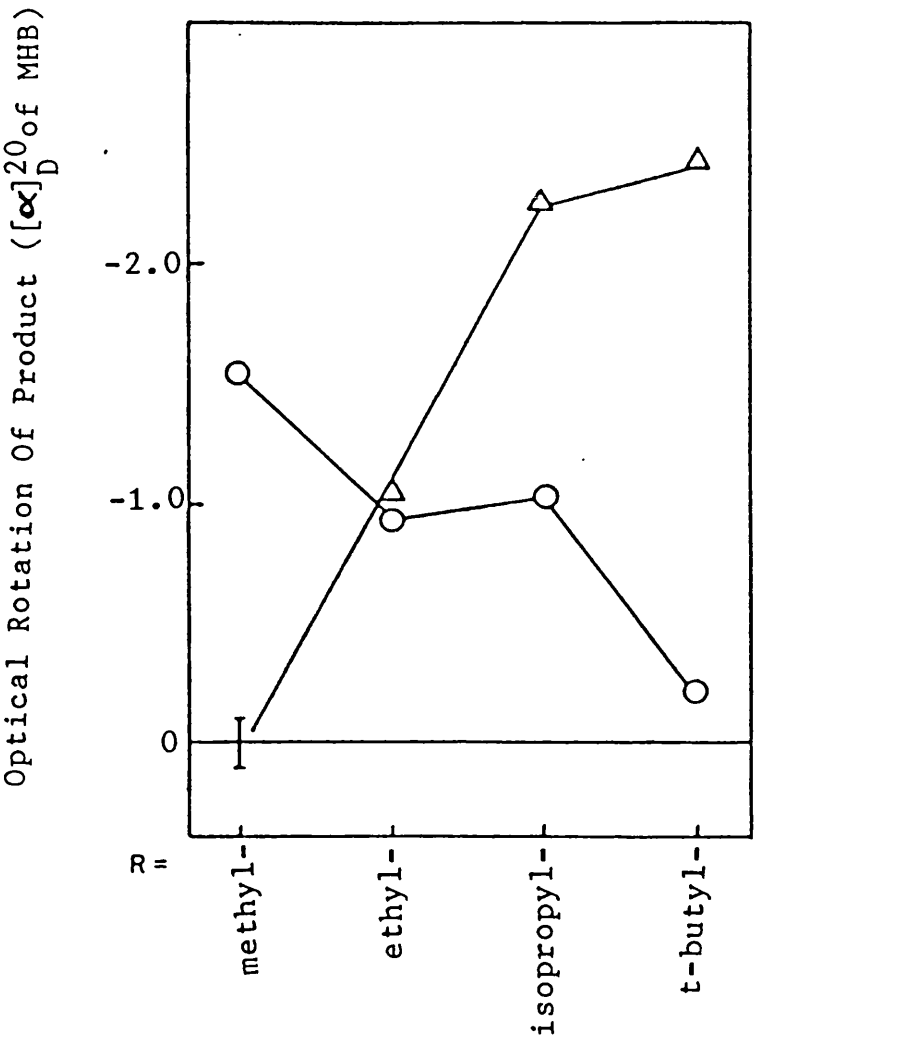
(S) malic acid

3. The nature of the 'Rg' group of the general structure Rg-CHX-CO_2H was also shown to be important; for amino acid modifiers, the larger the alkyl group the greater the enantioselectivity, where as in contrast, for hydroxy acid modifiers, increasing the length of the alkyl chain resulted in a decrease of enantioselectivity[54,55] (Figure 1.4.3b) in the resultant catalyst.

The presence of a second stereogenic centre (and the configuration at the centre) of the'Rg' group was

Figure 1.4.3b

The Effect Of The Alkyl Group (R) Of The Modifying Reagent R-CXH-CO_2H (X= -NH_2 or -OH) On The Enantio-Differentiating Ability Of The Resultant Catalyst.



also found to influence the enantiodifferentiating ability of the resultant catalysts. For example, optically pure tartaric acid proved to be a better modifier (i.e. increased optical yield) than compounds with a single stereogenic centre. The importance of the configuration at the second stereogenic centre is illustrated by the use of meso tartaric acid modified catalysts, which exhibited no enantioselectivity. The effect of the presence of a second stereogenic centre is shown in Table 1.4.3b:-

Table 1.4.3b

Modifying Reagent	$[\alpha]_D^{20}$	O.Y.(%)
(S,S) 2 hydroxy 3 methyl pentanoic acid[57]	+0.68	2.96
(S,R) 2 hydroxy 3 methyl pentanoic acid[57]	-0.22	0.96
(R,R) tartaric acid[58]	-6.0	26.1
(R,S) tartaric acid[58]	0	0

Taking account of the data generated, optically pure tartaric acid was proved to be the optimum modifying reagent for maximising the enantiodifferentiating ability of catalysts. It was also apparent at this time that the experimental conditions employed in catalyst modification and MAA hydrogenation influenced the the achievable optical yields with the resultant

modified Raney nickel catalysts[38,51]. In the next two sections (1.4.4 & 1.4.5) the development of the modifying procedure (using tartaric acid) and the hydrogenation conditions for optimising the enantiodifferentiating ability of nickel catalysts is described. The explanations of the effect of altering variables in these two sections are dicussed in Chapter 5, with reference to the findings of this study.

Section 1.4.4

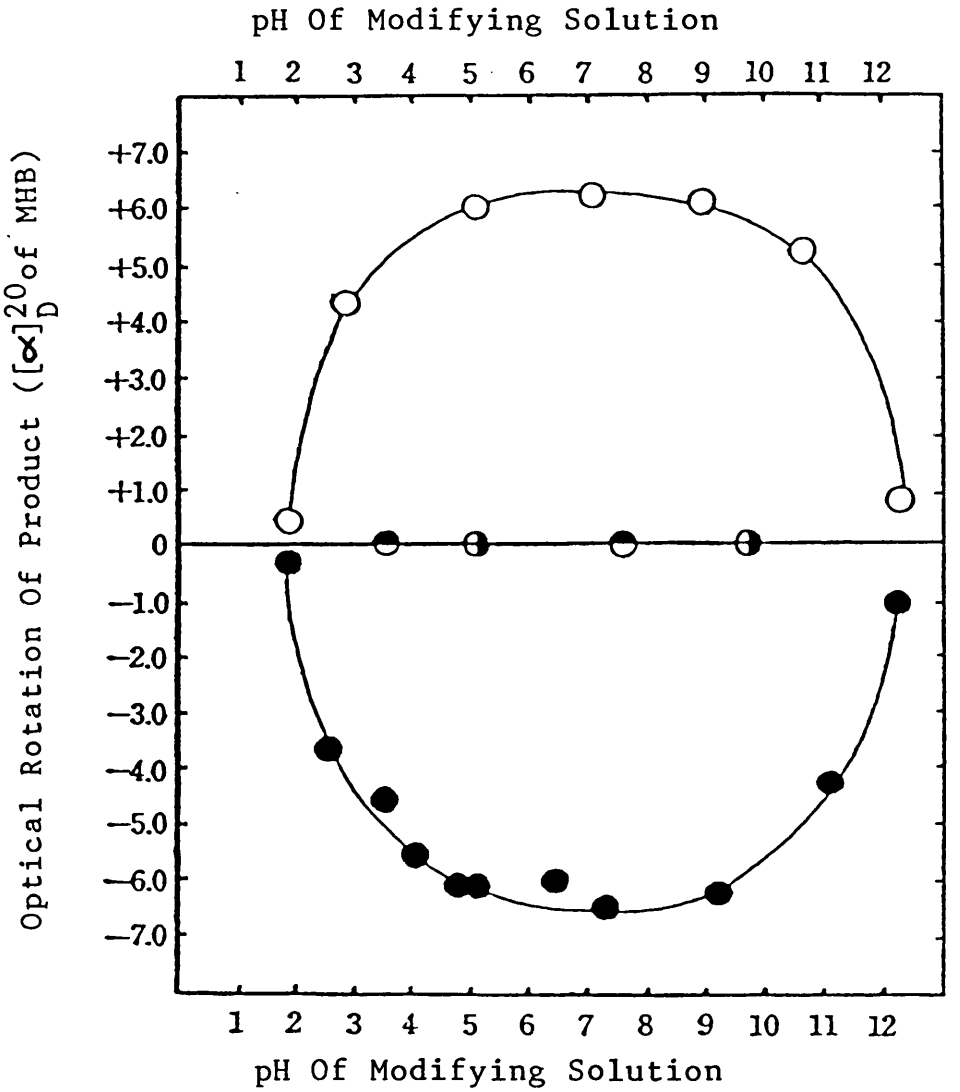
The Effect of The Modification Procedure on The Enantiodifferentiating Ability of Ni Catalysts.

In 1968, Tatsumi[58] reported his findings on the effect of the procedure of Ni catalyst modification by optically pure tartaric acid. While Izumi had observed a dependence of asymmetric catalytic behaviour on the pH of the modifying solution (5.1 being the optimum value), Tatsumi examined this effect in further detail and found enantiodifferentiating ability in the reduction of MAA by Raney Ni, modified over a wide range of pH values (Figure 1.4.4a). [This figure also illustrates the effect of using the different enantiomers of tartaric acid and the effect of using the meso or racemic forms].

The second variable of modification investigated was the modification temperature (T_{mod}); for catalysts modified by (S,S) tartaric acid the effect of increasing the temperature from 273 to 373 K was to increase the

Figure 1.4.4a

The Effect Of The pH Of The Modifying Solution / The Effect Of The Use Of Stereoisomers Of Tartaric Acid.



○ = (S,S) tartaric acid

● = (R,R) tartaric acid

◑ = meso-tartaric acid

◐ = racemic tartaric acid

enantiodifferentiating activity of the resultant catalyst (from O.Y. = 6 to 9 %), though the overall hydrogenation activity decreased. This was also the case for derivatives of tartaric acid[58] and a range of hydroxy monocarboxylic acids[53].

Tatsumi[58] also reported an optimum modification time (t_{mod}), when the other variables of modification were as follows:- [(R,R) tartaric acid]= 0.133 mol dm^{-3}, volume of modifying solution= 100cm^3, pH=5.0 and T_{mod}= 273 K. He found that for t_{mod} values as low as 2 minutes, high asymmetric activity was achieved which increased up to a t_{mod} value of 10 minutes. Prolonging t_{mod} beyond 10 minutes was shown to have little effect (Figure 1.4.4b).

Finally the effect of the concentration of the modifying reagent was considered by Tatsumi; the effect of increasing the concentration with respect to the optical yield of the product mixture is shown in Figure 1.4.4c:- this figure indicates that the enantio-differentiating ability of the modified catalyst is independent of the concentration of tartaric acid in the range 2.67×10^{-2} to 0.67 mol dm^{-3}.

This study by Tatsumi reinforced the idea that the modification procedure as well as choice of modifying reagent was governed to the asymmetric activity of the resultant catalyst. The conditions he described were used to modify catalysts in other studies, where the

Figure 1.4.4b

The Effect Of Modification Time On The Enantiodifferentiating Ability On Catalysts.

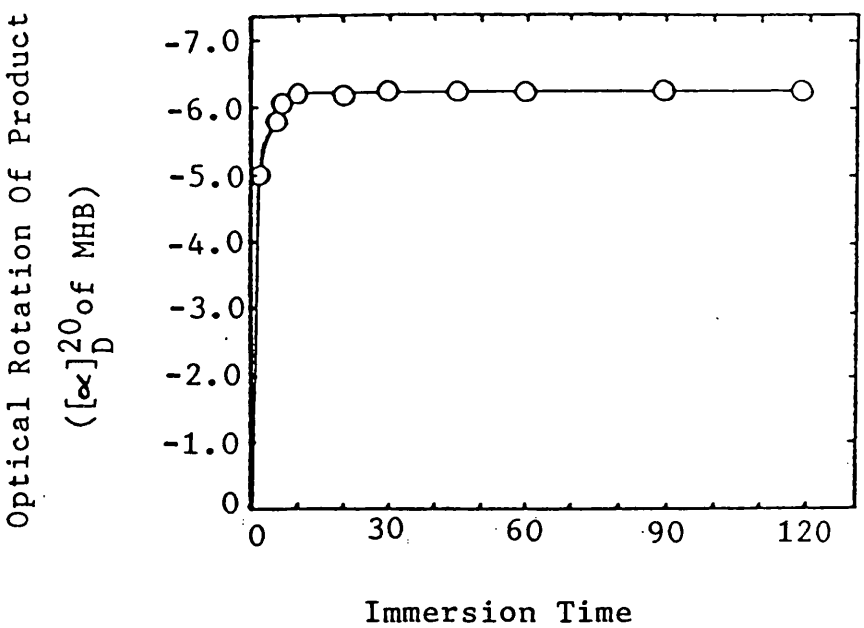
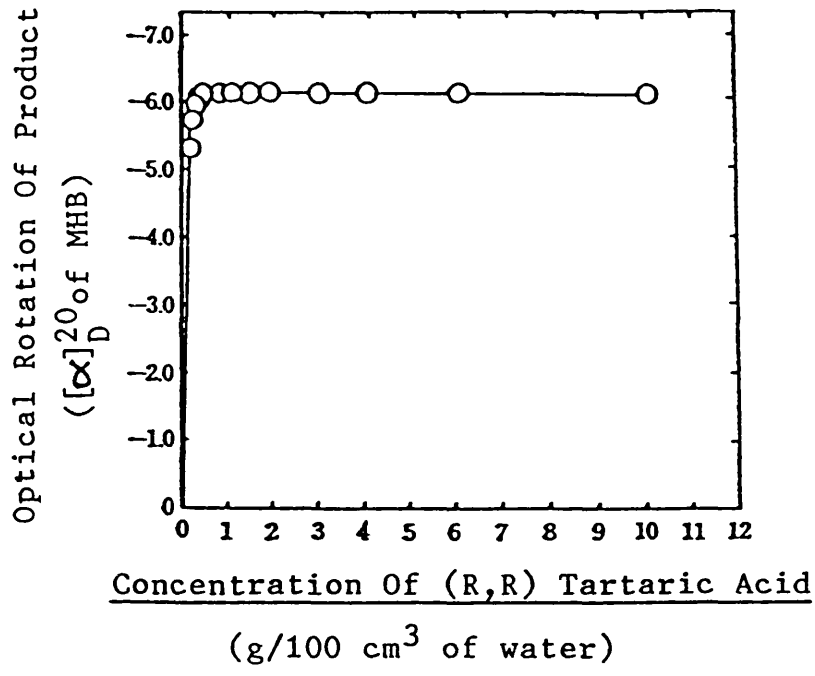


Figure 1.4.4c

The Effect Of Tartaric Acid Concentration.



modification step was not the major interest[63].

Typically the variables of modification in subsequent studies were as displayed in Table 1.4.4a-

Table 1.4.4a

Modifying Reagent	Modification Variables		
	Temperature	pH	Time of Immersion
Optically Pure Tartaric Acid	60,61 62 273 or 373K	60 5.1	60 1 hour
	Solvent (volume)		[T.A.]
	Water (100 cm^3)		1-2%[59]

The conditions listed in the above table differ slightly from the optimum conditions described by Tatsumi (e.g. time of immersion), but they are within the limits described by him not to be detrimental to the enantiodifferentiating ability of the modified catalysts. In the remaining part of this section, exceptions and additions in the development of the modification procedure as laid out by Tatsumi are described.

With regard to the modification pH, Klabunovskii et al.[64], reported O.Y. maxima for catalysts modified at pH 2 and 13 and Christie[22] found greatest enantiodifferentiating ability in Raney nickel catalysts modified at pH= 3.2. In some studies, a pH value other than the typical value was used, without explanation[67].

In addition to the importance of the initial pH, it

was also found that the choice of alkali hydroxide solution, used in pH adjustment, exerted influence on the optical yield of the product mixture. The greatest enantiodifferentiating ability was exhibited by catalysts that were modified in solutions which had the pH value adjusted with aqueous sodium hydroxide[66] (Figure 1.4.4d; this figure also illustrates the effect of temperature on asymmetric activity).

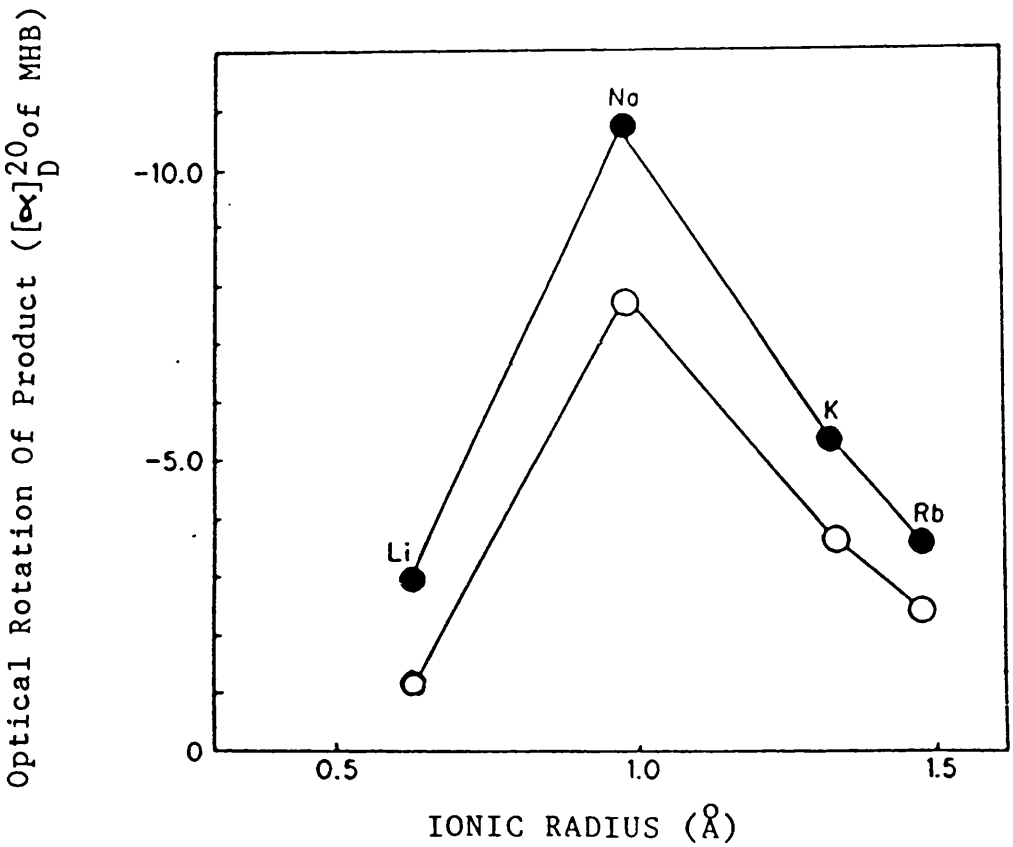
A new feature was introduced to the modification procedure in 1978 when Izumi and co-workers[65] used impure water (containing sulphate and chloride ions), accidentally, as the modification solvent and discovered an enhancement in the asymmetric behaviour of the modified catalysts. This led to the study of various metal salts to examine their effect as 'co-modifiers' during the modification procedure[65,67]. In particular, sodium salts were studied, as the beneficial effect on modified catalyst enantiodifferentiating ability due to the presence of sodium cations had already been demonstrated in studies concerning pH adjustment. The effect of various sodium salts and nickel bromide as co-modifiers is shown in Table 1.4.4b. The other details of modification were as follows:-

100 cm^3 of aqueous (S,S) tartaric acid (1g) solution; pH= 3.2; Temperature of modification = 373 K

The MAA hydrogenation conditions (the effect of these on

Figure 1.4.4d

The Effect Of The Alkali Hydroxide Used To Adjust The pH Of The Modifying Solution.



O; Modification Temperature= 273 K

●; Modification Temperature= 373 K

the asymmetric activity of modified catalysts is considered in the next section) were:-

A solution of MAA (11.5 cm^3) in methyl propionate (23 cm^3) and acetic acid (0.2 cm^3). Weight of catalyst= 0.8g Hydrogen Pressure= 90 Atm., Reaction Temperature= 373 K

Table 1.4.4b

Co-modifier	Concentration (mol dm^{-3})	O.Y.(%)
none	/	39.2
$NaH_2PO_4.2H_2O$	6.41×10^{-2}	35.7
Na_2SO_4	0.70	56.4
$NaNO_3$	1.18×10^{-2}	53.0
NaF	0.71	60.8
NaCl	1.71	72.1
NaBr	0.97	83.1
NaI	3.33×10^{-5}	51.2
$NiBr_2$	4.55×10^{-2}	62.6

These data clearly indicated the beneficial effect of a co-modifier component in catalyst modification and identified the best co-modifier as sodium bromide, the presence of which more than doubled the optical yield of the product mixture.

Another variation on the theme of catalyst modification was the use of nickel (S,S) tartrate and

nickel sodium tartrate complexes as the modifying reagents of Raney, supported and unsupported nickel catalysts. An initial non-descriptive report on this method by Yasumori et al.,[69] was followed up by Hoek and Sachtler[68] who found greater enantiodifferentiating ability of catalysts modified this way, than the conventional tartaric acid treatment. A comparison of catalysts modified with tartaric acid and the nickel tartrate complexes is given in Table 1.4.4c:-

Table 1.4.4c

Catalyst	Modification Temperature (K)	Modifying Reagent/e.e.(%)[c] H_2TA	NiTA	Na_2NiTA''
Ni powder	293	+9to+15	+40to+45	0[a]
Ni powder	393	+15to+25	+2 to+4[b]	+30to+35

a Complex not adsorbed
b Complex precipitates
c The range of e.e. values determined by experiment.

The nomenclature for the modifying reagents is that used by Hoek and Sachtler[68]:-

H_2TA= (S,S) tartaric acid; TA is the tartrate anion (both carboxyl protons dissociated); TA" is the tartrate anion with both hydroxyl protons dissociated

This table indicates that the nickel (and nickel/sodium) tartrate complexes are as effective as modifying reagents as tartaric acid, and that other conditions of modification (such as temperature) do not effect the extent of asymmetric activity in the same way for

different modifying reagents. These complexes were shown to have no catalytic activity when tested by Hoek and Sachtler[68].

Hoek and Sachtler[68] also gave details of another variable of modification that had not been considered before- the atmosphere above the modifying solution/ catalyst during modification. They found that a silica supported nickel catalyst (5% by weight Ni) had similar enantiodifferentiating ability when modified under hydrogen or nitrogen (modifying reagent=(S,S) tartaric acid,all other modification variables the same) but this increased by almost 3 times when a sample of catalyst was modified under air (Table 1.4.4d).

Table 1.4.4d

Catalyst	Temperature Of Modification(K)	E.E.(%)	
		Hydrogen	Air
Ni/SiO_2	293	+3 to +4	+9 to +10
Ni/SiO_2	373	+5 to +7	+17 to +18

In contrast, I. Yasumori et al.,[72] later found that increasing the oxygen content of the modification atmosphere decreased the enantiodifferentiating ability of a modified nickel powder catalysts [e.e.(%)= 48 (vacuum), 32 (air), 28 (oxygen)].

Hoek and Sachtler[68] also observed that during the modification procedure, the tartaric acid solutions

became green in colour, the intensity of which was increased for modification under air compared to under a hydrogen atmosphere. The colour of the solution was indicative of the presence of a dissolved nickel complex which they suggested was the result of the corrosive nature of catalyst modification. The effect of air on modification could be intensified, as shown by their[68] experiment of bubbling air through a nickel powder/ tartaric acid solution suspension to the extent that precipitation of the nickel complex occurred. However this effect has been ignored and not quantified, as has the fact that this process must reduce the metal composition of the catalyst from pre- to post-modification. In the research leading to the preparation of this thesis, the extent of corrosion has been measured by atomic absorption photometry (Section 3.2.3) and the results recorded in Chapter 4.

The final stage in the preparation of modified catalysts is the washing of the catalyst, necessary to remove residual unadsorbed modifier, co-modifier and any of the corroded nickel complex. Typically[22] the modified catalyst was washed with distilled water, followed by an organic solvent (methanol) and then the reaction solvent or a sample of the substrate (if no solvent was to be used in the hydrogenation reaction).

Section 1.4.5

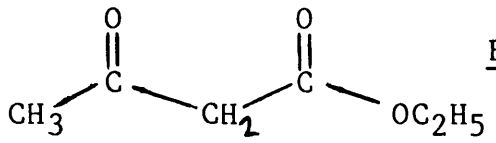
The Effect of Reaction Conditions on The Enantiodifferentiating Ability of Nickel Catalysts.

In asymmetric hydrogenation reactions over tartaric acid modified nickel catalysts, the reaction variables have been shown to exert considerable influence on the optical yield of the product mixture. These variables include temperature of reaction, hydrogen pressure, solvent, substrate/catalyst ratio, the presence of additives and the degree of conversion. In this section these variables are considered separately, showing maxima in O.Y. when all other conditions are constant.

Temperature

Klabunovskii[70] found that in the hydrogenation of Ethyl Acetoacetate (EAA Figure 1.4.5a)

Figure 1.4.5a



Ethyl Acetoacetate (EAA).

the enantiomeric excess passed through a maximum when the temperature of reaction was in the range 343-353 K, independent of the presence or absence of any solvent.

Izumi and co-workers [60,71,74], in their initial studies hydrogenated MAA at 333 K but in subsequent investigations they discovered a maximum in optical

yield at ca. 323 K (Figure 1.4.5b). This temperature was also reported as the optimum in the study of Smith and and Musoiu[62].

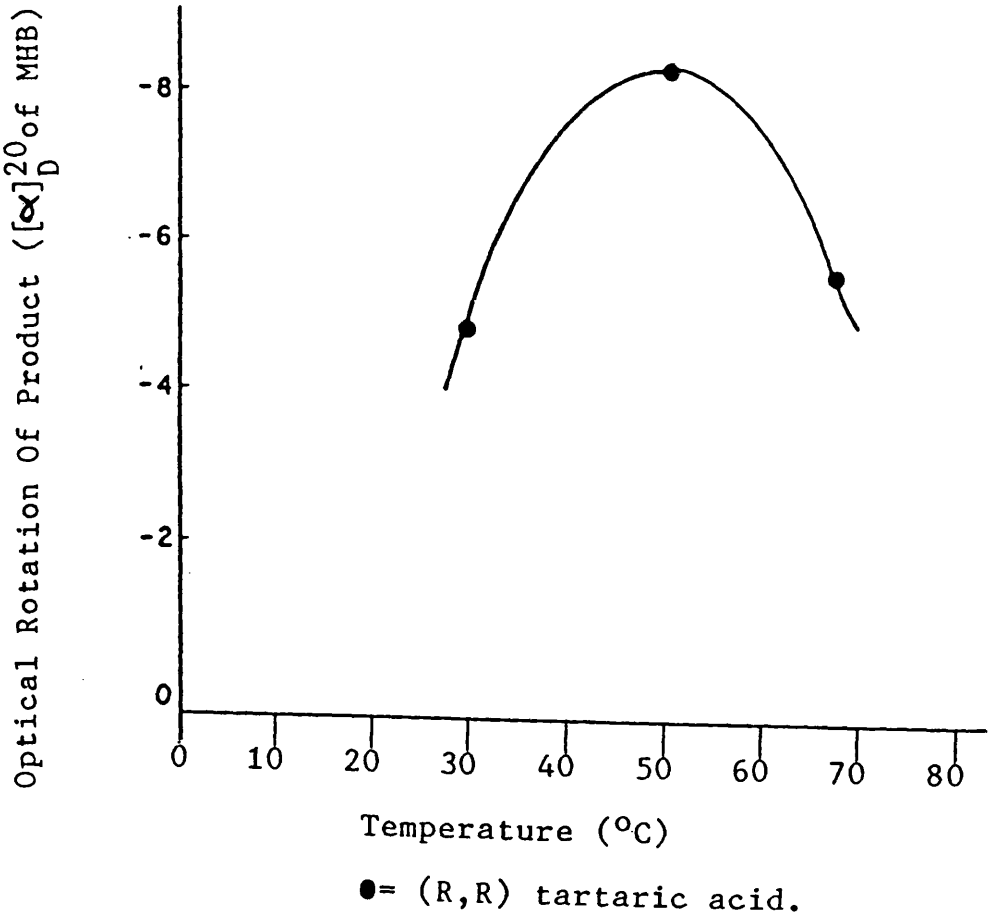
Hydrogen Pressure

The original studies by Izumi[25] involved the asymmetric reduction of MAA under hydrogen an initial pressure of 80 atmospheres. Further studies by other groups found a dependence of enantiodifferentiating ability on hydrogen pressure. Klabunovskii[73] found that in the asymmetric hydrogenation of EAA, there was a decline in the enantiomeric excess on increasing the hydrogen pressure from 1 atmosphere[60], but in the 25 to 100 atmosphere range the e.e. remained virtually constant. He also stated that the overall rate of reaction increased with hydrogen pressure up to 50 atmospheres and then remained constant. Also, the enantioselectivity of a reaction was extremely sensitive to the degree of catalyst/reaction mixture agitation in high pressure reactions. This finding suggests the presence of diffusion limitations (of hydrogen through the solvent to the catalyst surface), a feature which could be limited by operating in a sufficient agitation regime as illustrated by Nitta et al.[77].

Similarly to the work of Klabunovskii on modified Raney nickel, Nitta et al.[75] also reported a decrease in the optical yield of MHB in MAA hydrogenation over a

Figure 1.4.5b

The Effect Of The Temperature Of Hydrogenation Of MAA.



tartaric acid modified Ni:SiO_2 (1:1) catalyst, when the pressure was increased from 1 to 10 atmospheres. However, he also found that the optical yield increased again as the hydrogen pressure increased from 20 to 80 atmospheres[75], though to a level below that of the atmospheric pressure result (Figure 1.4.5c).

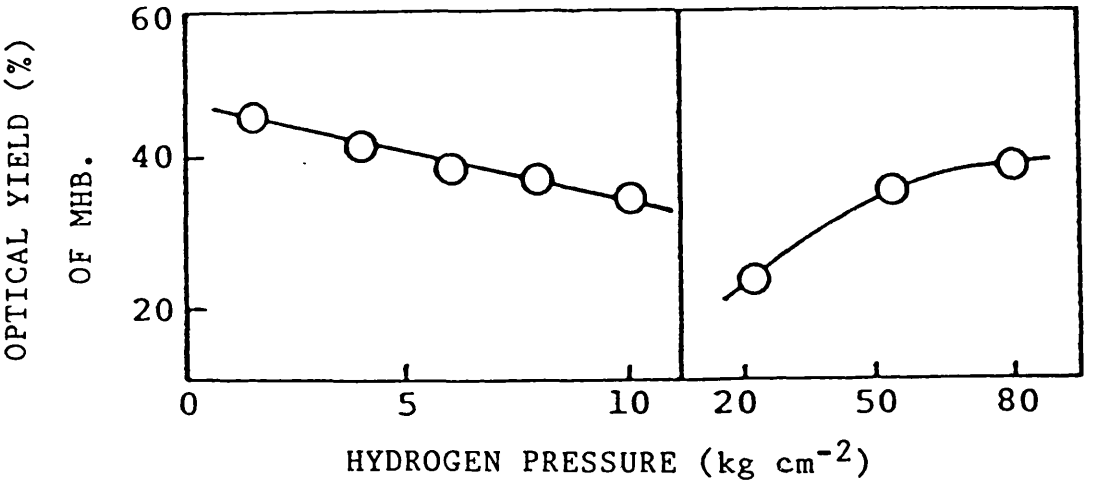
Solvent

While several studies have investigated the liquid phase hydrogenation of MAA neat[38,68], other studies have used solvents and found that solvent choice can effect the enantiomeric excess of the resultant product mixture. For example, Klabunovskii's[73,76] study of EAA hydrogenation showed that the best solvents for optimum e.e. values of product mixtures were anhydrous alcohols (methanol > ethanol > propanol), tetrahydrofuran and dioxane. The addition of water to these solvents greatly reduced the e.e.; 25:75 % water:ethanol mixture used as the solvent resulted in an e.e. value that was a quarter of that achieved with pure ethanol as solvent, a 50:50 mixture as solvent virtually removed all asymmetric activity. Klabunovskii demonstrated that these solvents gave better results than the organic solvents such as ethyl acetate, a solvent used by Izumi et al.,[60] and Nitta et al.,[75].

Nitta, however, reported a solvent effect when using ethyl acetate- increasing the concentration of MAA in

Figure 1.4.5c

The Effect Of Hydrogen Pressure On The Enantioselective Hydrogenation Of MAA.



the solvent increased the optical yield of MHB (Figure 1.4.5d). They also found this to be the case when the solvent used was methanol or tetrahydrofuran[77].

Substrate/Catalyst Ratio

In the hydrogenation of MAA over (S) glutamic acid modified Raney nickel, Izumi[51] recorded a maximum in the O.Y. when the substrate/catalyst ratio was approximately 30. Hubbel and Rys[63] performed MAA hydrogenation reactions with three different quantities of tartaric acid modified Raney Ni (0.025, 0.05, 0.10 g [starting Ni:Al alloy] cm^{-3} [MAA]), and found the highest initial optical activity in the product mixture from the intermediate substrate/catalyst value. Klabunovskii[73] also reported a relationship between the optical activity and the substrate/catalyst ratio for the asymmetric reduction of EAA; increasing the ratio increased the asymmetric yield towards a limiting value at high substrate/catalyst ratio (Figure 1.4.5e). In the studies of Smith and Musoiu[62], their results showed that below a substrate/catalyst ratio of 5:2 optical purities were low, but values above this ratio had no effect on optical purity.

Reaction Mixture Additives

The addition of small amounts of certain compounds has been shown to effect the asymmetric activity of modified nickel catalysts. For example, addition of

Figure 1.4.5d

The Effect Of MAA Concentration In The Enantioselective Hydrogenation Of MAA.

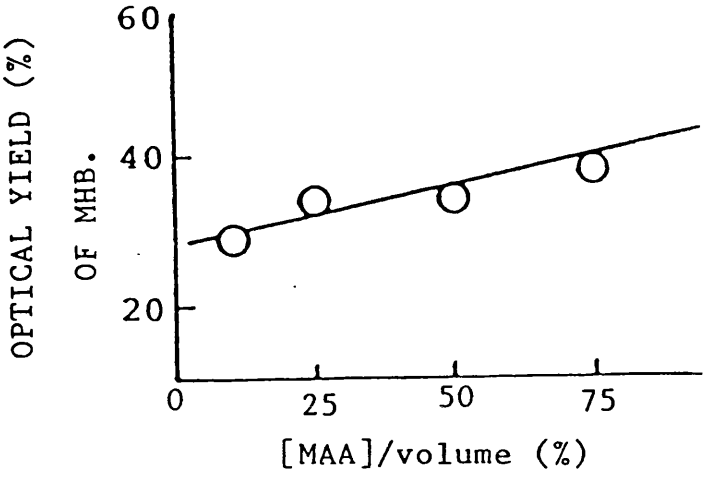
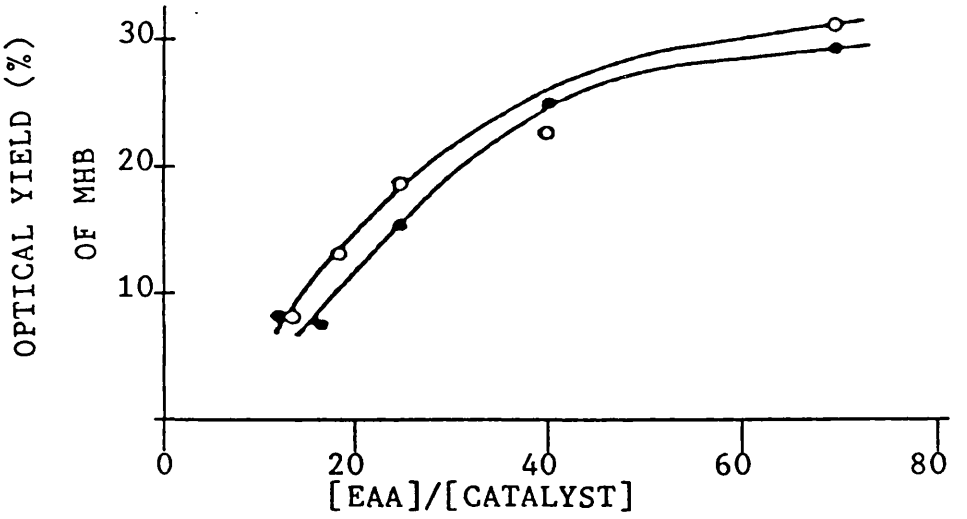


Figure 1.4.5e

The Effect Of Substrate/Catalyst Ratio In The The Enantioselective Hydrogenation Of EAA.



O= No Solvent

●= butan-1-ol used as the reaction solvent

water to the reaction solvent was detrimental to the e.e. for MAA hydrogenation over tartaric acid modified catalysts (Solvent subsection). [A more complicated effect was noted when water was the additive in amino acid modified systems[50]; the optical yield declined with increase in water addition and then increased in the opposite direction (i.e. from an excess of (R)-MHB to an excess of (S)+MHB[78,80].]

The optical yield was shown to increase when small quantities of acetic or pivalic acid were added to the reaction mixture. The enhancement in optical yield was only slight in the asymmetric reduction of MAA[79], but much more significant in the hydrogenation of prochiral octan-2-one[81,82].

$H_{13}C_6\text{-}C\text{-}CH_3$ octan-2-one.

The optical yield increased from ca. 2%(no pivalic acid) to ca. 60%(15 cm^3 pivalic acid added to the reaction mixture).

The third group of compounds used as additives were unsaturated hydrocarbons- cyclohexene, cyclo-octene, 2,3 dimethyl but-2-ene and benzene[77]. Increasing the mole fraction of the additives showed that the enhancement in the optical yield passed through a maximum. Benzene, which was not hydrogenated during the

reaction, proved to be the most successful additive (increasing the O.Y. from 54 to 78%) but when used as the reaction solvent O.Y. was diminished.

The beneficial effect of the presence of an alkali halide co-modifier during the modification was illustrated in the previous section. Bostelaar and Sachtler[83] added a range of these compounds (LiBr,NaBr, RbBr,NaI and KI) at various concentrations, not to the modifying solution, but to the reaction mixture, for hydrogenation over an 11 wt.% Ni/SiO_2 catalyst prepared and modified by their own method[84]. By this method of introduction of the co-modifier, they showed that for increasing NaBr concentration there was a maximum in the e.e. which declined at higher NaBr concentrations, though hydrogenation activity remained relatively constant. The iodide salts also increased the e.e. to approximately the same as NaBr, but the enhancement was for a narrower concentration range; for KI, NaI, the e.e. increased from ca. 42% to 60% as salt concentration increased from ca. 1×10^{-4} to 1×10^{-3} mol dm^{-3}, then fell to 0 as the concentration of co-modifier increased to approximately 4×10^{-2} mol dm^{-3} c.f. NaBr e.e. increased with concentration (1×10^{-3} to 4×10^{-2} mol dm^{-3}) to 60% but declined only slightly (5-10%) at higher concentrations. The activity of catalyst samples modified with iodide salts dropped to 0 as concentration

increased from ca. 1×10^{-4} to 4×10^{-2} mol dm-3.

Extent Of Reaction

According to Hubbel and Rys[63], the optical yield of the product mixture varies with the extent of reaction. The optical yield remained constant during MAA hydrogenation up to a mole fraction of MHB of 0.8, then dropped by ca. 10%. Due to this variation some studies determined the optical yield of the product mixture at low conversion levels of MAA e.g. Harada et al.,[60] stopped hydrogenation before 40% conversion. Other studies though determined enantiomeric excesses upon complete reduction of MAA[22,68].

Section 1.4.6

The Effect of The Nature And Preparation Conditions of Nickel Catalysts on Their Post-Modification Enantiodifferentiating Ability.

Section 1.4.2 contained a general description of the type of Ni catalysts that have been used in asymmetric hydrogenation reactions; however for individual types of catalyst, differences outside the general description have been shown to effect the enantiodifferentiating ability (post-modification):-

Raney Nickel

In 1974, Gross and Rys[85] reported variation in the obtainable optical yields for Raney nickel catalysts of different pre-modification hydrogenation activity. The activity of catalyst samples was varied by altering the conditions of the ingestion of the Ni/Al alloy in aqueous sodium hydroxide, and individual samples were assigned an activity rating from the W-scale by Gross and Rys with reference to the work of Augustine[86]. The W-scale assignments of each of the Raney Ni samples they studied and the alloy (30g of Ni:Al [50:50]) ingestion conditions (aqueous NaOH [5 mol dm^{-3}]) are given in Table 1.4.6a.[In the activity assignments, W-0 is the least active Raney nickel sample and W-6 is the most active.]

Table 1.4.6a

Catalyst Assignment	Initial Temperature Of NaOH Solution K	Ingestion Temperature K	Time[a]
W-0	278-283	Reflux	1440
W-1	278-283	Reflux	240
>W-1	278-283	Reflux	75
>W-2	353	353	50
W-6	323	323	50

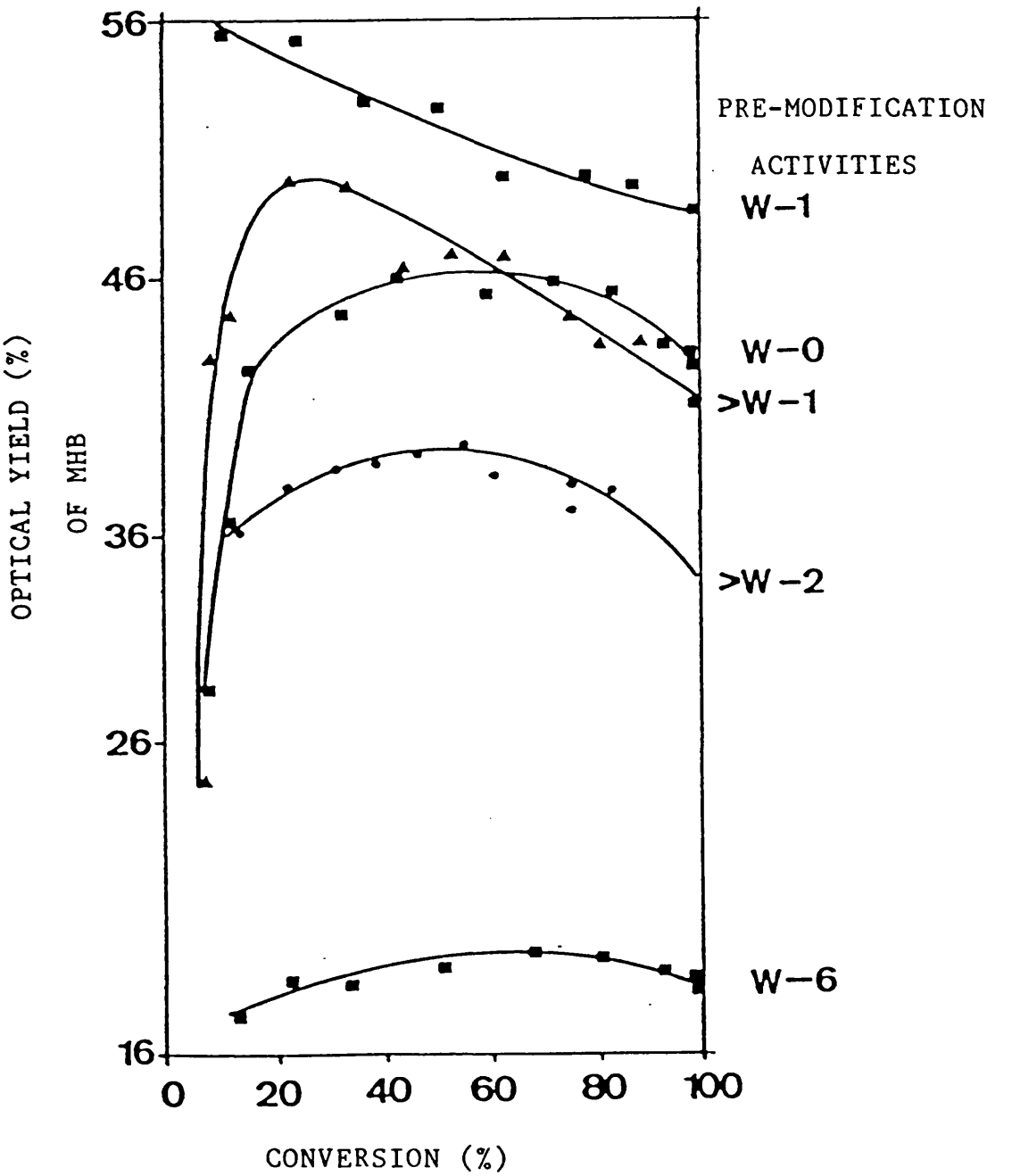
a minutes.

In their study, Gross and Rys illustrated variation of the optical yield with extent of reaction, as Hubbell and Rys had reported earlier[63]. However they showed that this variation was dependant on the pre-modification activity of the Raney nickel and that increasing this activity (with the exception of W-0) lowered the maximum in the optical yield of the product mixture (Figure 1.4.6a).

As mentioned previously(Section 1.4.2), Raney nickel is not pure nickel, containing variable quantities of residual aluminium and hydrated alumina. Harada et al.[87] highlighted the possibility of these impurities influencing the enantiodifferentiating ability of modified catalysts. In a later study[67] they reported the enantiodifferentiating ability of modified Raney nickel catalysts, prepared under identical conditions,

Figure 1.4.6a

The Effect Of The Initial Activities Of Raney Nickel On The Enantioselective Hydrogenation Of MAA.



from three different starting alloys- Ni:Al, Ni:Mg and Ni:Si. The results using these alloys are given in Table 1.4.6b:-

Table 1.4.6b

Catalyst Precursor (Raney Alloy)	e.e.[1] from resultant modified catalyst(%)
Ni:Al[a]	44
Ni:Mg[a]	6
Ni:Si[a]	44
Ni:Al[b]	30

1. e.e. of product mixture of MAA hydrogenation
a. pH of modification adjusted to 5.0 with NaOH
b. pH of modification adjusted to 5.0with $NaAlO_2$

By comparing of the results shown in Table 1.4.6b to the results from a modified nickel powder catalyst (prepared by hydrogenolysis of NiO) which gave a greater e.e.(59%), Harada concluded that the presence of Al, Mg or Si was detrimental to the asymmetric activity of the resultant catalyst. Harada emphasised the negative effect of Al by using $NaAlO_2$ to adjust the pH of modification in one experiment (Table 1.4.6b).

A feature of the Ni:Al alloy used to prepare Raney Ni not described in Section 1.4.2 is that the alloy consists of distinct metal phases-$NiAl_3$, Ni_2Al_3 and NiAl

the proportions of these phases being related to the total Ni:Al ratio. Each of these phases has been shown to have different reactivities towards ingestion in aqueous NaOH[41], so alloys of non-identical phase composition result in Raney Ni catalysts of differing Al content, surface area and crystallite size[88]. Consequently, the resultant catalysts (pre-modification) exhibit variation in catalytic activity[89,90].

As the effect of residual Al and initial catalytic activity has already been illustrated in this section, the choice of starting Raney alloy, in terms of phase composition, would therefore be expected to influence the enantiodifferentiating ability of a resultant modified catalyst. This was found to be the case in the study of the asymmetric hydrogenation of EAA by Klabunovskii et al.,[91]. They found that by decreasing the nickel content of the starting alloy from 50 to 38.3%, the phase composition ($NiAl_3$:Ni_2Al_3) changed from 10:90 to 51.2:48.8; of the resultant modified catalysts, the sample produced from the starting alloy of 51.2% $NiAl_3$ had the highest catalytic activity and enantiodifferentiating ability.

Nickel Powder Catalysts.

Nickel powder catalysts have not been studied to the same extent as Raney nickel in asymmetric hydogenation,

but the presence of impurities in these catalysts and preparative variations have been shown to effect enantio -differentiating ability. Harada[67] noted that there was a relation between the colour of the NiO powder used to prepare the catalyst and the subsequent e.e. values of product mixtures; a 'light green' NiO resulted in a modified catalyst with greater enantiodifferentiating ability than a sample prepared from 'dark green' NiO, the colour being related to the level of impurities. Therefore the origin of the NiO used was important, but as these catalysts are Al and Al_2O_3 (the main impurities of Raney Ni) free, Harada expected them to exhibit higher enantiodifferentiating ability than modified Raney Ni which he found to be the case[67,92].

Nickel powder catalysts, supplied commercially, have been shown to exhibit higher enantiodifferentiating ability when they were activated under hydrogen gas prior to modification[42,43].

Supported Nickel Catalysts.

Hoek and Sachtler[68] studied supported Ni (5% by weight) catalysts prepared by impregnation of the support material (silica or alumina) by aqueous nickel nitrate solutions. They found that while silica supported catalysts exhibited similar enantioselectivity to nickel powder catalysts, the use of alumina as the support greatly reduced this ability of nickel

catalysts. To investigate if the supports catalysed a secondary racemisation reaction, pure (S)-+-MHB was stirred with samples of the supports for 16 hours, after which time the optical activity was unchanged. Hoek and Sachtler linked the detrimental effect of alumina (as a support) to the findings of Harada[87] on the effect of residual Al (as Al_2O_3) in Raney nickel. Harada also studied the use of nickel catalysts on various supports in asymmetric hydrogenation reactions (Table 1.4.6c):-

Table 1.4.6c

SUPPORT	O.Y.(%)
KIESELGUHR[a]	
Shimalite SP-17	54
Shimalite SP-25	44
Shimalite SP-35	37
Shimalite SP-55	38
ACTIVATED ALUMINA	
Woelm acidic	67
W 200 basic	68
W 200 neutral	68
TiO_2	70
ZrO_2	63

a Shimalite SP-17 is an unpurified Kieselguhr; the others were purified by acid and/or alkali washing.

In this study the nickel:support ratio was 1:1, though no further detail of catalyst precursor preparation was included in the report. However, the results for alumina supported catalysts illustrated a metal loading effect when viewed with those of Hoek and

Sachtler; increasing the metal load (from 5[68] to 50%[67]) increased the enantiodifferentiating ability of nickel/alumina catalysts. Harada assigned the higher O.Y. of the product mixture from the unpurified Kieselguhr over the others as due to the impurities acting as co-modifiers in the same fashion as NaBr.

A more comprehensive study of the use of modified supported nickel catalysts was performed by Nitta et al.,[47]. They investigated a range of supports (SiO_2, Al_2O_3, TiO_2, MgO, kieselguhr and zeolite), nickel salts (nitrate, acetate and sulphate), preparative methods (impregnation and precipitation), nickel loading and reduction conditions. The outcome of this study was that highest optical yields were achieved when a Ni:SiO_2 catalyst precursor of high metal loading (50%) was prepared by a specific precipitation method using nickel nitrate and sodium carbonate, and reduced under set conditions prior to modification. By controlling these variables the mean crystallite size ($\overline{D}c$) and crystallite size distribution (C.S.D.) of the resultant unmodified catalyst could be fixed, considered by Nitta to be necessary to increase the enantiodifferentiating ability of the resultant modified catalysts. In conclusion, Nitta stated that for supported catalysts the higher the value of $\overline{D}c$, the higher the enantioselectivity of the resultant modified catalyst and that a narrow C.S.D. of

nickel particles around 10 nm was also important; the given explanation being that smaller crystallites with high specific activity and low selectivity have a large contribution to overall hydrogenation and hence lower the optical yield. This was in accordance with a previous study by Nitta[93] on increasing enantiodifferent -iating ability with particle size for unsupported catalysts, a phenomenon he ascribed to the need for large ensembles of regularly arranged nickel atoms on the catalyst surface for strong and regular adsorption of the tartaric acid modifier.

Fu, Kung and Sachtler[94] also studied supported nickel catalysts with a view to determining any effect of nickel crystallite size on enantiodifferentiating ability of modified catalysts. The method of control of crystallite size used in their study was the process known as 'Ostwald ripening'[95] which causes larger Ni particles to grow at the expense of smaller particles and involves reacting the reduced nickel catalyst with carbon monoxide:-

$$Ni + 4\ CO \rightleftharpoons Ni(CO)_4$$

followed by decomposition of the carbonyl complex; the carbonyl is formed from particles of high free energy and decomposes on particles of low free energy[96], resulting in growth of the larger particles. By this method (and by varying ripening time), catalysts of

different average particle size (measured by hydrogen chemisorption and X ray diffraction) up to 10 nm were produced. Modifying each of these catalysts in the same way and using them in the asymmetric hydrogenation of MAA, did not reveal an apparent crystallite size effect as the work by Nitta had.

An interesting feature of this study by Fu et al.[94] was that it was one of the few published papers to comment on the corrosive nature of catalyst modification by tartaric acid and report the extent of corrosion. The extent of corrosion caused by altering modification conditions is given in Table 1.4.6d:-

Table 1.4.6d

CATALYST SAMPLE	MODIFICATION VARIABLES (a) T(K)	Time(hours)	Volume(cm^3)	Ni loading* (wt.%)
1	UNMODIFIED			11.3
2	293	2	20	10.3+/-0.3
3	293	13	20	9.5+/-0.1
4	373	2	100	5.8+/-0.3

(a) The tartaric acid solution was 0.133 mol dm^{-3}, pH= 5(adjusted with aqueous NaOH)
* Post-Modification.

With respect to crystallite size, they asserted that there was no particular effect on enantiodifferentiating ability except that particle size must be sufficient to withstand corrosion; smaller particles were completely leached during the modification step.

Section 1.4.7 Asymmetric Hydrogenation Over Tartaric Acid Modified Nickel Catalysts; The Diversity of Data.

In Sections 1.4.2 to 1.4.6 the development of the experimental procedure for the asymmetric hydrogenation of MAA over tartaric acid modified nickel catalysts has been described in terms of optimising conditions that were shown to influence the stereochemical outcome of the reaction. However, it should be noted that the data is taken from several independent sources- hence suggested optimum values were derived from a non-standard basis. For example, the study of modification conditions by Tatsumi[58] identified maxima for several of the variables but little consideration was given to the choice of initial alloy and preparation conditions, though these were shown to be important in later reports[85,88]. A more specific example of the non-standard basis of reported results is that given by Sachtler[83] in his study of the effect of alkali halides. In this study e.e. was enhanced by up to 60% on addition of NaBr(for an 11% by wt. Ni/SiO_2 catalyst) compared to a value of 80% for Raney nickel[65,67], however the hydrogenation of MAA over the modified Raney nickel catalyst was performed at higher temperature, hydrogen pressure and to a higher conversion level of MHB.

Despite the complex preparation considerations,

nickel catalysts modified by optically pure tartaric acid have proved to be very efficient in the asymmetric hydrogenation of MAA. Optical yields as high as 90% have been reported[65], and attempts to discover the definitive asymmetric catalyst preparation and MAA hydrogenation conditions have had some success[22].

In conjunction with improvements in the experimental procedures, kinetic and mechanistic models have been proposed for the asymmetric hydrogenation of MAA which are described in the next two sections.

Section 1.5 The Kinetics And Mechanism of Enantioselective Hydrogenation.

In the examples of non-selective synthesis given in Section 1.2.7 (hydrobromination of an alkene and carbonyl hydrogenation) it was illustrated that equality in the activation energy for the production of each enantiomer resulted in a racemic mixture. Therefore it was assumed that in asymmetric processes, a difference in the quantities of enantiomers produced was the result of non-equivalent activation energies leading to each. While this is true for some reactions (e.g. the diastereoselective reaction of (+)-arabinose with HCN[22]) studies have shown that activation energies in the reduction of MAA are the same for both tartaric acid modified and unmodified catalysts (Table 1.5a):-

Table 1.5a

CATALYST	REACTION PHASE	HYDROGEN PRESSURE	ACTIVATION ENERGY(kJmol^{-1})[60,97]
Ni powder* unmodified	gaseous	100-300 torr	44.3+/-2.5
Ni powder* modified	gaseous	100-300 torr	43.9+/-2.1
Raney Ni modified	liquid	760 torr	43.9+/-2.1

* The nickel powder catalyst was prepared from nickel formate.

As activation energy was uneffected by modifying the catalyst, and independent of the type of amino or

hydroxy acid modifier[60], Izumi[98] assumed that the activation energies of hydrogenations of the si- and re-enantiofaces of MAA (Section 1.2.7) must be the same. Thus he concluded that the enantioselective behaviour of a modified catalyst was the result of a preferential interaction of one face of the carbonyl with the modified catalyst (e.g. (R,R)-+-tartaric acid modified catalyst preferentially interacts with the si-enantioface of MAA to give an excess of R(-)MHB). Various mechanisms have been proposed to describe this interaction which leads to the asymmetric and symmetric (as there are no reports of 100% enantioselectivity, MAA must also be reduced non-selectively) hydrogenation activity of tartaric acid modified nickel catalysts by all the main groups working in this area of study, which are given in the next section.

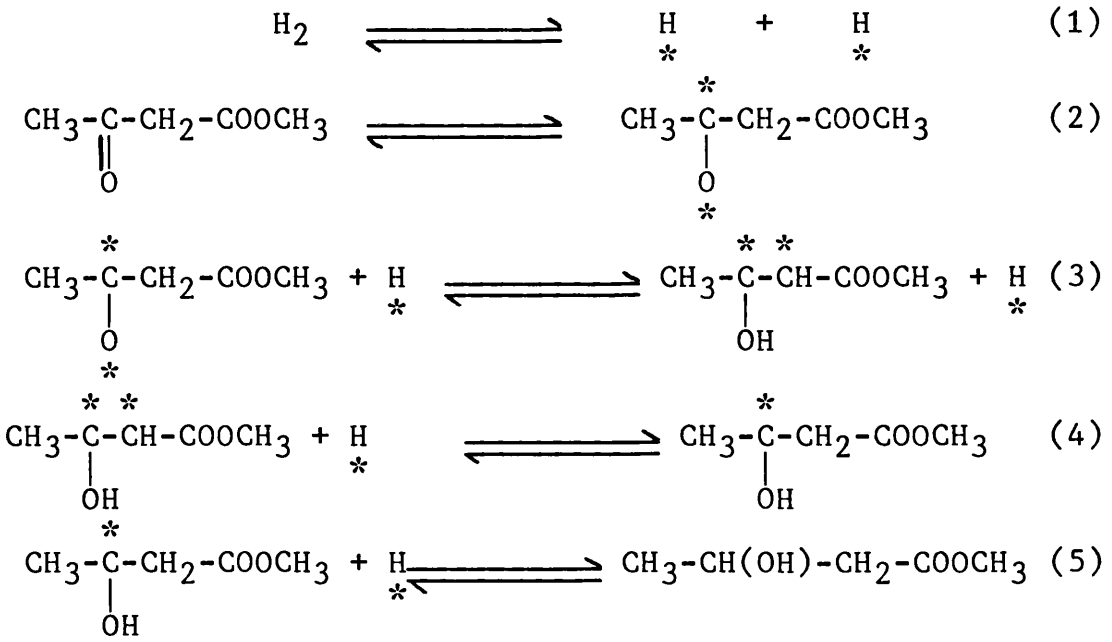
More detailed consideration of the kinetics of enantiodifferentiating catalysis, is given in reports by Klabunovskii[70] and by Nitta et al.,[93].

Section 1.5.1 The Proposed Mechanisms of Enantio-Diffferentiation by Tartaric Acid Modified Ni Catalysts

Mechanism I

The mechanism proposed by Yasumori, Yokozeki and Inoue[72] was based on their[44] X-ray photoelectron spectroscopic (X.P.S.) study on the adsorbed state of

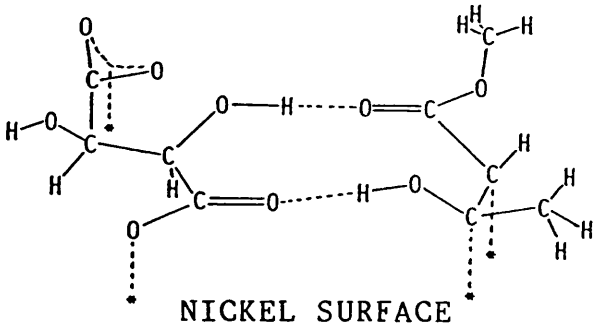
tartaric acid, which they found to be adsorbed by the two carboxylate groups. This information was in agreement with infra-red studies which also indicated the formation of surface carboxylates[99,100]. The adsorbed tartrate anion controlled the stereochemistry of the adsorbed substrate through hydrogen bonding (Figure 1.5.1a) with hydrogenation proceeding by the following proposed reaction sequence:-



*=adsorption site

In their proposed mechanism, it is worth noting that the enantioselectivity results from hydrogen bonding of the adsorbed tartrate to the adsorbed enol tautomer of the substrate, MAA. (That is enantiodifferentiation occurs when the species on the right hand side of (3) above interacts with adsorbed tartaric acid).

Figure 1.5.1a



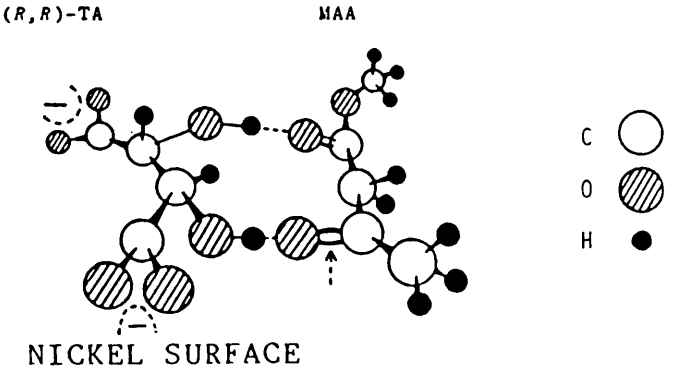
The adsorbed MAA, of controlled stereochemistry was then hydrogenated, the rate determining step being (5).

However this mechanism offered no explanation to the beneficial effect of a NaBr co-modifier, or why there was incomplete stereoselectivity (e.e.= 48% in their report[72]).

Mechanism II

This mechanism was proposed by Izumi[98] and co-workers and again the mode of interaction between the tartaric acid modified catalyst and MAA which resulted in enantio -differentiation was hydrogen bonding. The modifier was assumed to be adsorbed to a flat nickel surface and hydrogen bonded to MAA as shown in Figure 1.5.1b[101,102].

Figure 1.5.1b



The main difference to the proposed mechanism of Yasumori is that the substrate is represented by its keto-form as it had been shown that methyl 2,2-dimethyl acetoacetate (which could not form the suggested adsorbed enol) was asymmetrically hydrogenated to the same extent as MAA[62]. Originally their model assumed hydrogen addition from the nickel surface, but later they proposed a new hypothesis for hydrogenation of the substrate[98,103] which can be summarised as follows:-

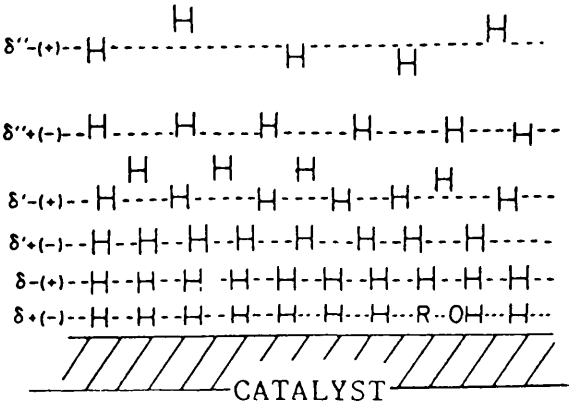
(i) A monolayer of hydrogen is chemisorbed on the nickel surface, on top of which there are layers of physically adsorbed hydrogen.

(ii) The polarization induced by the chemisorbed hydrogen can be transmitted through the physically adsorbed layers, with polarizable substances (e.g. alcohols) acting as transmitters.

(iii) The hydrogenation of MAA, i.e. of the polarizable carbonyl group, can take place anywhere in the layer of polarized hydrogen.

This model of polarized hydrogen is represented schematically in Figure 1.5.1c:-

Figure 1.5.1c



On the basis of this hypothesis, Izumi concluded that hydrogenation of MAA occurred where the stereogenic centre caused enantiodifferentiation, away from the the surface of the catalyst. Thus high enantiodifferentiation was the result of greatest overlap of layers of polarised hydrogen with sites where the differentiation took place.

This group also offered an explanation for incomplete stereoselectivity in modified Raney nickel catalysts, and a reason for improvement of enantiodifferentiation with the inclusion of NaBr as a co-modifier. They reported[92] that on addition of NaBr to modifying solutions the amount of tartaric acid adsorbed decreased slightly then held steady with increasing [NaBr] (NaBr also reached a maximum adsorbed value). From this they concluded that the catalyst surface consisted of at least two parts; one that preferentially adsorbed tartaric acid, the other NaBr. The part of the catalyst surface that adsorbs tartaric acid is the area where enantioselective hydrogenation occurs, while the other part, thought to contain the aluminium impurities detrimental to selectivity, adsorbs NaBr - poisoning the area responsible for racemic hydrogenation. In this model of enantioselective catalysis, incomplete stereoselectivity was considered to be the result of incomplete poisoning; the area of non-selective

hydrogenation being further divided into two regions, one of which adsorbed NaBr and another which did not and was responsible for non-selectivity.

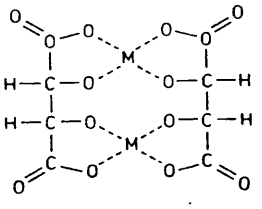
Model III

The third model for the enantiodifferentiating mechanism of tartaric acid modified nickel catalysts was that proposed by Sachtler et al. In their model it was proposed that the formation of a nickel tartrate complex on the surface of the catalyst (produced by corrosive chemisorption) was the site of enantiodifferentiation. This model differed from the previous two, which involved interaction of modifier and substrate on a flat nickel surface, in that Sachtler's model of complex formation used the concept of corrosive chemisorption- a term which describes the process of adsorbate and adsorbent metal atom moving out of the original lattice site with subsequent re-arrangement of the remaining metal (this is an activated process, though thermodynamically more stable above a minimum surface coverage[104]). Sachtler assumed that nickel tartrate formation was necessary for enantiodifferentiation, on the basis of the results he got on modifying nickel catalysts with such complexes[68].

The initial proposed structure of this complex was taken to be that of other binuclear tartrates[105], the

structures of which are represented schematically in Figure 1.5.1d. Sachtler felt that this binuclear complex was probably Ni/Na tartrate, as an explanation to the beneficial effect of using NaOH over other alkali hydroxides to adjust the pH of modification.

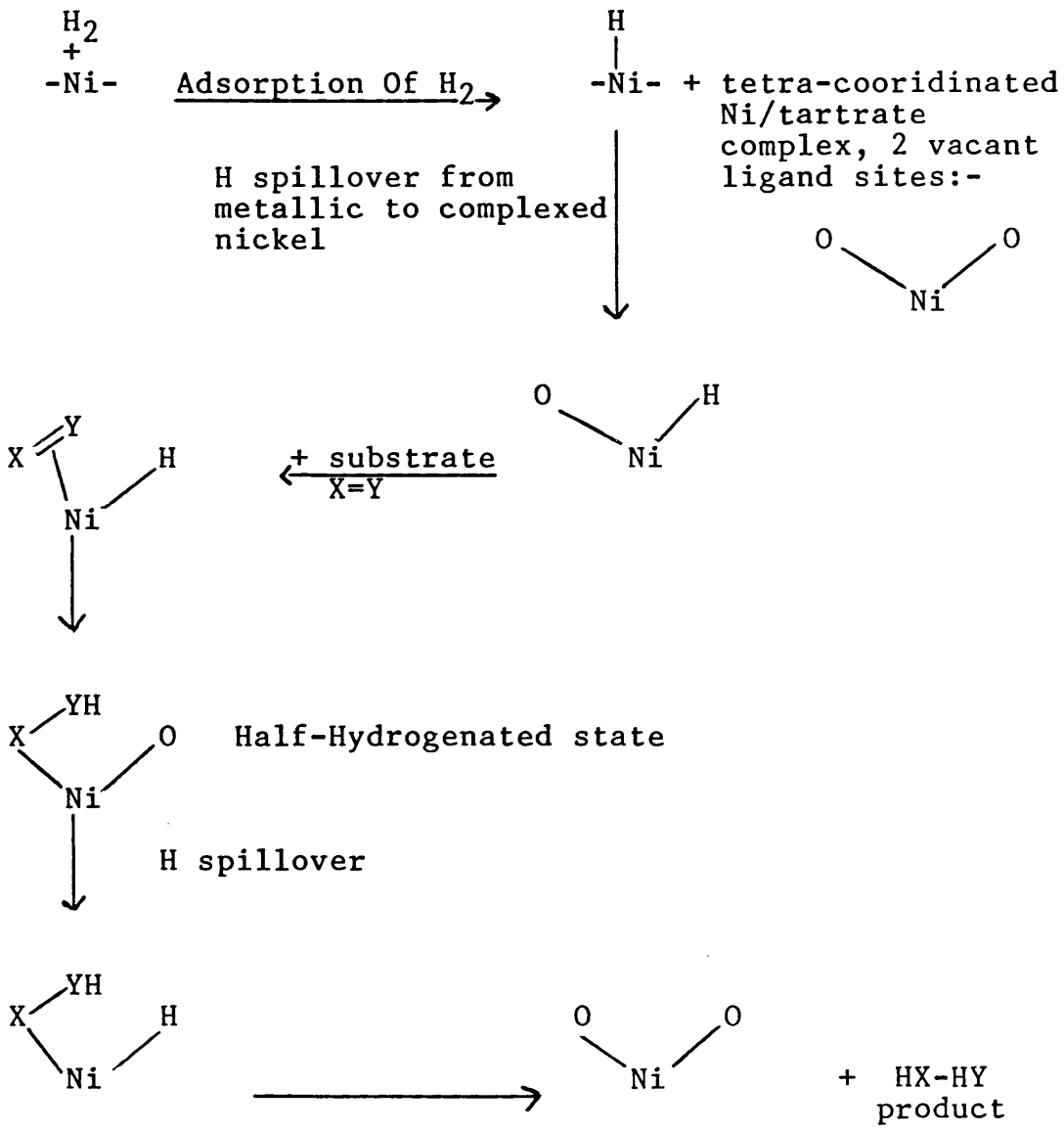
Figure 1.5.1d



Further to this he specified that this essential complex (which had no hydrogenating ability itself[68]), had to be adsorbed on the nickel surface which dissociated hydrogen gas to the chemisorbed atoms; Sachtler then assumed that the substrate was adsorbed on one of the two vacant sites of the tetra-coordinate Ni complex and hydrogenated by means of spillover[106] via the tartrate ligands. This mechanism is illustrated in Figure 1.5.1e with the absence of the tartrate ligands- these would control the preferential adsorbtion of one substrate face, giving enantiodifferentiation. It is worth noting that in this mechanism it is also the keto form of MAA that is hydrogenated; Sachtler had found in I.R. studies that MAA was adsorbed as the enol[107],

Figure 1.5.1e

A Proposed Mechanism For The Enantioselective Hydrogenation Of MAA.



but concluded that the active form is different from the stable form identified spectroscopically because of the results of methyl 2,2-dimethyl acetoacetate reduction.

In Sachtler's mechanism, the detrimental effect of alumina (residual in Raney nickel or as a support) on enantioselectivity was explained as a combination of racemic hydrogenation on the alumina surface, and strong adsorption of the modifier/nickel complex on the alumina leaving metallic nickel surfaces insufficiently modified. This mechanism was proposed from a study[68] that did not include the use of NaBr as a co-modifier, however they later studied the effect of NaBr and concluded that its primary function was not as a poison. They suggested that addition of NaBr to the modifying solution shifted the equilibrium position as defined by the solubility product (i.e. K_s, the equilibrium constant of a sparingly soluble salt), meaning that the amount of complex formed that was washed into solution was reduced[108]. Thus NaBr addition increased the amount of adsorbed Ni tartrate complex on the nickel surface, enhancing the enantiodifferentiating ability of the catalyst. The explanation given for incomplete stereoselectivity in catalysts with no alumina is that there are bare nickel atoms not disrupted from the lattice by tartaric acid which are responsible for racemic hydrogenation.

The basis of this model, i.e. the corrosive chemisorption of tartaric acid and the formation of an adsorbed complex which can be washed into the modifying solution, is strenghtened by the observations of Sachtler and co-workers[94] of the presence of a nickel II species in solution after modification and reduction of actual metal load of the modified catalyst, mentioned previously (Section 1.4.6).

Section 1.6 Other Studies of Asymmetric Heterogeneous Catalysis.

In this section a description of other studies using tartaric acid modified nickel catalysts (for example, the hydrogenation of substrates other than MAA) and asymmetric reactions involving other metal/modifier heterogeneous systems is given.

Section 1.6.1 Asymmetric Hydrogenation of Substrates Other Than MAA.

As highlighted in previous sections by reference to the reported work of Klabunovskii[70], the most studied alternate substrate (used in reduction) has been EAA. A comparative study of related substrates by Izumi[98] (Figure 1.6.1a) revealed a slight increase in optical yield for EAA (88%) over MAA (84%) but further increase in the carbon chain length of the alcohol residue of the

ester had little or no effect on O.Y. (Table 1.6.1a).

Figure 1.6.1a

CH_3COCH_2COOR (MAA, EAA; $R=CH_3$, $R=C_2H_5$)

Table 1.6.1a

Substrate (As Figure 1.6.1a) R	PRODUCT Configuration	O.Y.(%)
CH_3	R	84
C_2H_5	R	88
$CH_3(CH_2)_2$	R	88
$CH_3(CH_2)_4$	R	88
$CH_3(CH_2)_5$	R	88
$(CH_3)_2CH$	R	85
$(CH_3)_2CHCH_2$	R	88

Similarly, there was only slight variation in optical yield on altering alkyl chain length of the acid residue of the ester[98] (Figure 1.6.1b):-

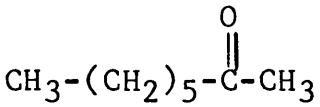
Figure 1.6.1b

$RCOCH_2COOCH_3$

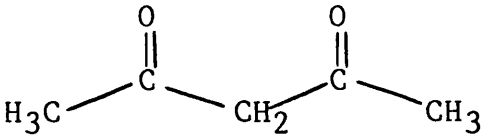
$R=CH_3$, O.Y.=85%; $R=CH_3(CH_2)_{12}$, O.Y.=87%

Substrates of structures other than the standard beta keto-ester form have also been hydrogenated over tartaric acid modified nickel catalysts. These are the ketone, octan-2-one[43] and the diketone, acetyl acetone[59] (pentan-2,4-dione), shown in Figure 1.6.1c.

Figure 1.6.1c



octan-2-one



pentan-2,4-dione

The study of the asymmetric reduction of the monoketone was reported by Osawa, Harada and Tai[43], and similar to MAA hydrogenation they reported that choice of reaction solvent influenced the O.Y. of product- tetrahydrofuran giving best results. A different feature of octan-2-one hydrogenation reported was the necessity of additives to the reaction mixture. Optical yields of less than 10% were recorded when octan-2-one (7.4 cm^3) was hydrogenated in THF (16 cm^3) but addition of increasing amounts of pivalic acid (Figure 1.6.1d), from 0 to 25g (0.245 moles) increased O.Y. to ca. 55%. Another necessary additive was found to be sodium pivalate (0.032g).

Figure 1.6.1d

$(CH_3)_3CCO_2H$

For octan-2-one reduction increasing the temperature of reaction from 313 K to 433 K reduced the enantio-differentiating ability of the modified catalyst from 80 to 20%, while for MAA hydrogenation over a catalyst prepared in the same way, O.Y. remained constant over this temperature range. By way of comparison, Osawa et

al.[109,110] also tried other monoketones as substrates for asymmetric hydrogenation, the results of which are shown in Table 1.6.1b.

Table 1.6.1b

Substrate	Optical Yield (%)		Configuration Of Product
	373 K (a)	363 K (a)	
Butan-2-one	49	63	S
Hexan-2-one	66	80	S
Heptan-2-one	66	71	S
Octan-2-one	66	80	S
Decan-2-one	58	76	S
Octan-3-one	14	-	S
Octan-4-one	6	-	S

(a) Reaction Temperature.

As is shown in the above table tartaric acid modified nickel catalysts exhibit good enantiodifferentiating ability in the reduction of monoketones providing the keto group is in the '2' position.

The study of acetyl acetone hydrogenation by Tanabe[59] concerned the corrosive effect of the substrate on the nickel catalyst. He found that modification of the nickel surface reduced the amount of corrosion i.e the amount of nickel removed from the surface to form a diketo complex of the type Ni(acetyl acetone)$_2$[111]. He also found that the hydrogenation of the first carbonyl group of acetyl acetone gave a very similar

asymmetric yield to that for MAA. From this he concluded that keto-enol tautomerism[112] of a substrate is not an important feature of the enantioselectivity process because of the difference in keto/enol equilibrium constants of each substrate.

Section 1.6.2 Acid Pretreatment of Raney Nickel.

In an attempt to limit the amount of residual aluminium, and thus reduce racemic hydrogenation, Izumi et al.,[92] reported the effect of acid pretreatment of Raney nickel prior to modification. This acid pretreatment involved stirring freshly prepared Raney Ni in tartaric or glycolic acid solutions of pH=3.2 (i.e. a pH lower than that they used in modification[113]). This method proved successful in removing part of the residual aluminium- with an accompanying increase in the enantiodifferenting ability of the resultant catalyst. A further effect of this acid treatment was corrosion of nickel, detected as Ni II, which Izumi speculated came from the same vicinity as the aluminium and was the site of non-selective hydrogenation. However this pretreatment did not completely remove aluminium, and did not become a common practice for producing asymmetric catalysts in later studies.

Section 1.6.3 The Effect of Additives to Catalyst Precursors on Enantiodifferentiating Ability.

In Section 1.4.6, the use of different starting alloys (Ni:Al, Ni:Si and Ni:Mg) for the preparation of Raney nickel, and the effect of the residual non-nickel components was described. Some studies have developed the idea of the effect of small amounts of additives further, adding materials to supported nickel catalysts in the hope of an enhancement of enantiodifferentiating ability. Orito et al.,[114] reported that Ni:Pt:kieselguhr catalysts (1:0.01:1) exhibited greater activity and enantioselectivity than the Ni:kieselguhr catalyst. No details of this promoting effect of platinum was offered and it was known that tartaric acid modified palladium, platinum or ruthenium catalysts showed only low enantiodifferentiating ability[115,116].

Nitta et al.,[117], who had reported that for supported nickel catalysts, consideration of the crystallite size distribution of the catalyst was important for maximising enantioselectivity (Section 1.4.6) felt that the beneficial effect of platinum was due to its stimulatory action in nickel reduction. This was based on the report of Roman and Delmon[118] who found that the presence of copper, palladium and platinum increased the rate and extent of silica supported nickel oxide

reduction. Nitta[47,119] studied a Ni:Pd:Silica catalyst (1:0.01:1) catalyst prepared by a precipitation method, the palladium content of the catalyst being added in the form of an aqueous solution of $PdCl_2$. Nitta found that both the trace metal and halide altered the structure of the catalyst and had an effect on O.Y. Increasing the palladium content of the catalyst decreased the enantiodifferentiating ability of the catalyst linearly, as did the amount of surface adsorbed tartaric acid. However, Pd addition did give better results than a Ni/silica catalyst when the reduction conditions used were mild (Table 1.6.3a).

Table 1.6.3a

Catalyst	Reduction Temperature (K)	Optical Yield (%)
Ni/SiO_2	573	23.9
Ni/SiO_2	623	35.9
$Ni/Pd/SiO_2$	573	27.8
$Ni/Pd/SiO_2$	623	36.5

Nitta explained that Pd stimulated reduction of $NiCO_3$ species under these conditions, resulting in a slight increase in mean crystallite size and optical yield. Nitta also showed that the presence of chloride also increased mean crystallite size, but he also found that

Ni/silica catalysts, reduced under optimum conditions had greater enantiodifferentiating ability and hydrogenation activity than catalysts with traces of Pd. Nitta concluded, that while trace elements effect nickel reduction, their presence decreases the size of ensembles of regularly arranged surface nickel on which enantiodifferentiation and the asymmetric hydrogenation can take place.

Section 1.6.4 Other Examples Of Heterogeneous Asymmetric Catalysis.

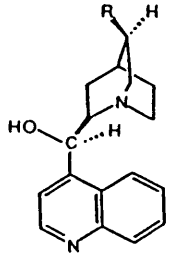
The other main area of study in asymmetric heterogeneous catalysis has been the hydrogenation of alpha-keto esters over platinum catalysts modified with alkaloids. In particular, the reduction of methyl pyruvate (Figure 1.6.4a) over a Pt catalyst modified in an ethanolic solution of cinchonidene (Figure 1.6.4b)[120].

Figure 1.6.4a

$CH_3COCO_2CH_3$

methyl pyruvate

Figure 1.6.4b

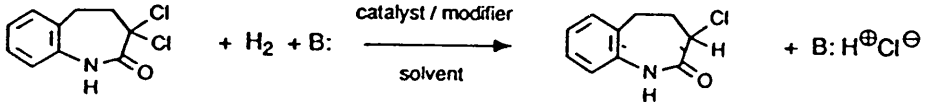


cinchonidene

This modified catalyst system exhibits a great deal of enantiodifferentiating ability, with reports of O.Y. in excess of 80%[121].

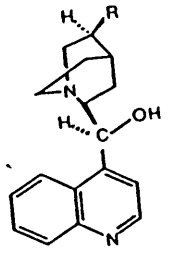
Although asymmetric heterogeneous hydrogenation reactions are the most widely studied, the possibility of heterogeneous catalysts to be used in other types of stereoselective reaction exists as illustrated by a report by Blaser et al.,[122]. They found enantiodifferentiation in the hydrodehalogenation of alpha,alpha-dichlorobenzazepinone (Figure 1.6.4c):-

Figure 1.6.4c



Where the conditions that gave the best results were- a $Pd/BaSO_4$ (5:95) catalyst, cinchonine modifer (Figure 1.6.4d), tetrahydrofuran solvent and the Lewis base tributylamine as the HCl acceptor B:. This system resulted in an enantiomeric excess of the product of 50%.

Figure 1.6.4d



cinchonine

CHAPTER TWO

OBJECTIVES OF THIS STUDY

The objective of the research described in this thesis was to gain further insight into the asymmetric hydrogenation of methyl acetoacetate to methyl 3-hydroxy butanoate over supported nickel catalysts modified by solutions of tartaric acid and sodium bromide, in particular, the study of Ni/SiO_2 catalysts modified in accordance with the methods proven to be successful for Raney nickel, accompanied with any necessary alterations to the modification procedure to enhance the asymmetric activity of the supported nickel catalysts.

To achieve this objective, this study is centred on the following:-

(a) Identification of the optimum conditions for the reduction of Ni/SiO_2 catalyst precursors for use in enantiodifferentiating hydrogenation.

(b) Determination of the effect which the various variables in the modification procedure have, not only on the resultant asymmetric activity of the catalyst, but also the physical effect on the catalyst.

(c) The development of an experimental apparatus and procedures to achieve the in-situ reduction and modification of Ni/SiO_2 catalysts, and the hydrogenation of MAA.

(d) Determination of methods for the quantitative analysis of the product mixtures using chromatographic techniques (G.C., H.P.L.C.) and Polarimetry.

CHAPTER THREE

EXPERIMENTAL

Section 3.1 INTRODUCTION

In this chapter the genesis of silica supported nickel enantiodifferentiating catalysts and the catalytic procedure for the asymmetric hydrogenation of methyl acetoacetate, MAA, (Fig 1.1.1) to an excess of the (R) enantiomer of methyl hydroxybutanoate, MHB, (Fig 1.1.1) are described in sequential steps.

The first of the steps involved the preparation of catalytic precursors, of various metal loading, by impregnation of the silica support with aqueous solutions of $Ni(NO_3)_2 . 6H_2O$. The next stage is catalyst activation, firstly by reducing the nickel (II) salt to nickel (0) in a flow of hydrogen gas and then modifying the reduced catalyst in aqueous solutions of (R,R)-+- tartaric acid. The modified catalyst then exhibits enantiodifferentiating ability in favour of the (R) enantiomer of MHB.

In the third section the apparatus and procedure for catalyst activation and MAA hydrogenation are described. The preparation and modification of Raney nickel under optimum conditions[22] is also included for comparative purposes.

The final part of this chapter is concerned with analysis of the product. The conversion of MAA to MHB

was determined by chromatographic methods, initially by Gas Chromatography and latterly by High Performance Liquid Chromatography. The analysis for MHB was used in conjunction with the measured angle of rotation of plane polarised light (Polarimetry) of the reaction mixture to calculate the enantiomeric excess (e.e.). The enantiomeric excess is defined as

$$(e.e.)_{\%} = \frac{[\text{ R-(-)-MHB }] - [\text{ S-(+)-MHB }]}{[\text{ R-(-)-MHB }] + [\text{ S-(+)-MHB }]} \times 100$$

The enantiomeric excess calculated from this data is a measure of the enantiodifferentiating ability of the catalyst used.

Section 3.1.1.a

The Preparation of Silica Supported Nickel Catalysts.

Silica supported nickel catalysts of approximately 1, 10, and 30 % w/w nickel loading were prepared by impregnation of a silica (non-porous microspheroidal Cab-O-Sil 5M, surface area 194 m^2g^{-1}) with aqueous solutions of $Ni(NO_3)_2 . 6H_2O$ (Aldrich 99.999%) of appropriate concentration.

For example, the 10% w/w nickel/silica catalyst was prepared as follows. A known volume of distilled water (0.25 dm^3) was added to Cab-O-Sil (90g) in a 1 dm^3 round bottomed flask to form a slurry, and to this 0.25 dm^3 of a ca. 0.7 mol dm^{-3} solution of $Ni(NO_3)_2 . 6H_2O$ was added.

The resultant suspension was stirred using a rotary-evaporator to achieve uniform mixing, and the water was then slowly evaporated under vacuum with continual mixing to incipient wetness. The catalyst precursor was further dried in an oven at 373 K for 16 hours. After drying, the catalyst precursors were sieved to a mesh size of 150-125 microns.

Section 3.1.1.b

The Preparation of a Silica Supported Ni/Pt Catalyst.

A silica supported Ni/Pt catalyst of approximately 10% Ni, 0.1%Pt was prepared by the method described in

Section 3.1.1.a. The Pt content of the precursor was added to the aqueous slurry of Cab-O-Sil in the form of an aqueous solution of hexachloroplatinic acid, H_2PtCl_6, (0.025 dm^3 of a ca. 2.0×10^{-2} mol dm^{-3}).

Section 3.1.2

Determination of The Nickel Content of The Ni/SiO_2 Catalysts.

Catalyst samples of known weight (ca. 0.2g) were ingested in 20 cm^3 of an aqueous 40% HF solution (BDH, AnalaR) at room temperature for 8 hours. The solution was then filtered and diluted to 250 cm^3 with distilled water.

The nickel content of these solutions, corresponding to the three prepared catalyst precursors, was determined by atomic absorption spectrophotometry using a Perkin Elmer 1100B Spectrophotometer fitted with a Cathodeon Ltd. hollow cathode lamp, suitable for detecting nickel; nickel absorption was measured at 232 nm.

Measurements were made in the 0 to 5 p.p.m. nickel concentration range. Standard solutions were prepared by dilution of a BDH Ltd. Spectrosol nickel nitrate stock solution (1000 p.p.m.). A typical calibration graph is is shown in Figure 3.1.2a where absorption (arbitary units) is plotted against p.p.m. nickel.

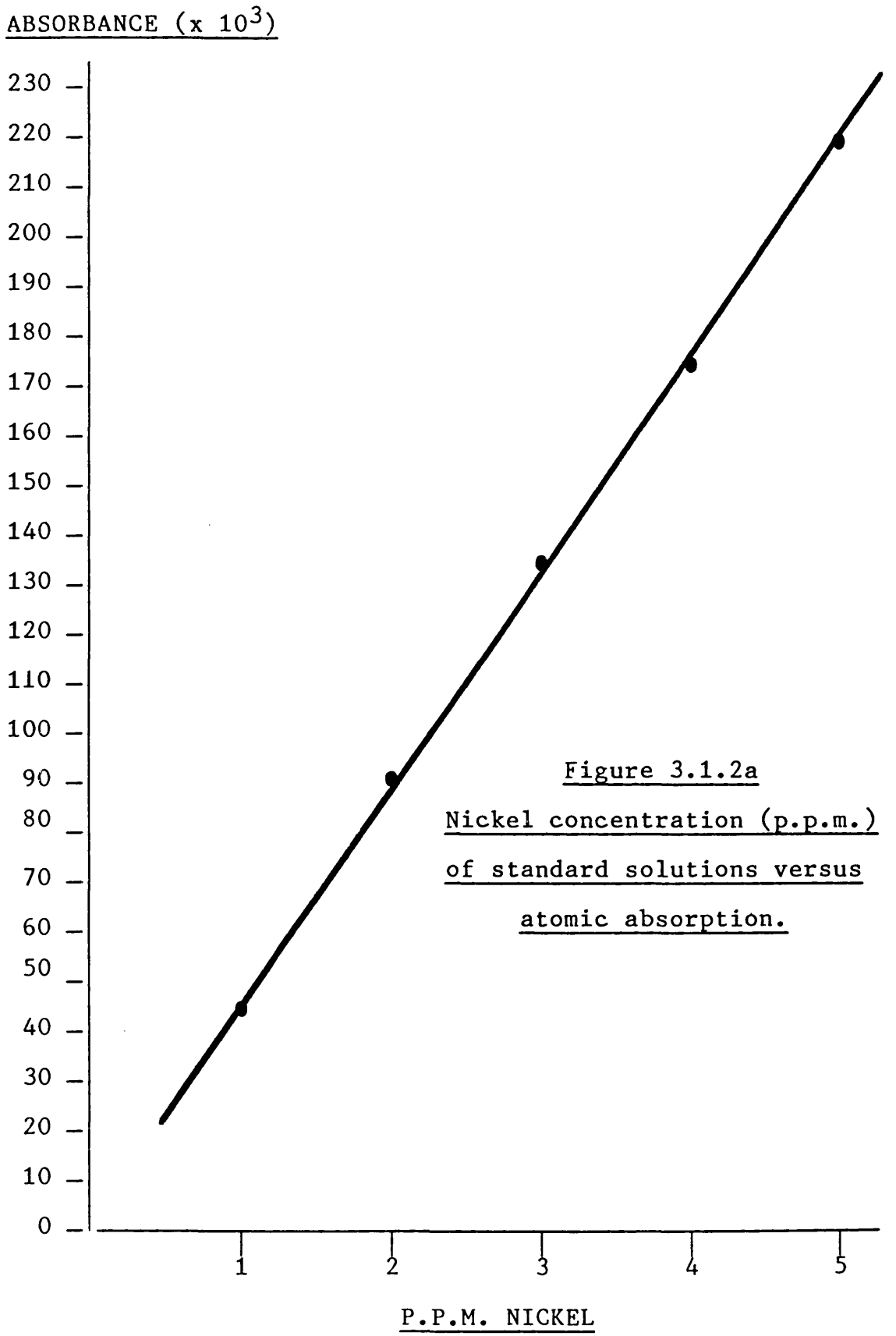


Figure 3.1.2a

Nickel concentration (p.p.m.) of standard solutions versus atomic absorption.

Where appropriate, catalyst sample solutions were diluted, so that the absorbance of the solution fell within the calibrated region.

The actual metal loadings of the catalyst samples is shown in Table 3.1.2a

Table 3.1.2a

CATALYST	% W/W Ni	$\frac{[Ni(NO_3)_2 . 6H_2O] \text{ mol dm}^{-3}}{(Cab\text{-}O\text{-}Sil)\ g^{-1}}$
[a]Ni/SiO_2 (I)	10.6	3.73×10^{-3}
[b]Ni/SiO_2 (II)	30.5	1.45×10^{-2}
[b]Ni/SiO_2 (III)	1.3	3.40×10^{-4}

a: 100g of catalyst precursor prepared.

b: 50g of catalyst precusor prepared.

Thermal analyses were conducted on the prepared sample using a Pye Unicam Thermobalance in the TG mode to measure water loss as a function of increasing temperature; water content was less than 5% for each sample.

Section 3.1.3

The Preparation of an Unsupported Nickel Catalyst: Raney Nickel.

Known weights (1.90g) of a 50:50 Ni:Al Raney alloy were added to a 5 mol dm^{-3} aqueous NaOH solution (20 cm^3) which was cooled in an ice bath to 273 K. The suspension was then heated to 373 K in an oil bath and maintained at this temperature for 1 hour, after which time the alkaline solution was decanted and the Raney Ni catalyst washed with distilled water (15 x 30 cm^3). Prior to modification, the catalyst was stored under distilled water.

Section 3.2 Catalyst Activation.

Pretreatment And Reduction of The Ni/SiO_2 Catalyst Precursors.

The catalytic reactors and glass high vacuum apparatus used in these stages of catalyst preparation are described in Section 3.3.

A sample of the appropriate Ni/SiO_2 catalyst (1g) was loaded into the catalytic reactor and pretreated by heating in vacuo at 10 K min^{-1} to a final temperature of 723 K which was maintained for 1 hour.

After the calcination step, the reaction vessel was allowed to cool to ambient temperature before the catalyst was reduced by again heating at a rate of 10 K min^{-1} to 723 K in a 150 cm^3 min^{-1} flow of hydrogen gas; these conditions (temperature and hydrogen flow rate) were maintained for a further 16 hours.

After reduction, the catalyst sample was out-gassed for 1 hour at 723 K and then cooled in vacuo.

Section 3.2.1 Catalyst Activation.

Modification of The Reduced Ni/SiO_2 Catalysts by Tartaric Acid / Sodium Bromide.

The freshly reduced catalyst samples were modified in 100 cm^3 aqueous solutions of optically pure (R,R)-+-tartaric acid and sodium bromide. The amount of tartaric acid was varied in the range 0 to 1g and sodium bromide in the range 0 to 10g.

Prior to catalyst modification, the pH value of the modifying solution was measured by a Pye Unicam Model 78 pH meter and adjusted to the required value (3.2,5.1,9) by the dropwise addition of 1 mol dm^{-3} aqueous sodium hydroxide solution for crude adjustments and 0.01 mol dm^{-3} aqueous sodium hydroxide for fine adjustments to the pH.

The catalyst sample was then stirred vigorously in the modifying solution for 1 hour at temperatures in the range 273-373 K.

After the catalyst had been modified, the modifying solution was removed and stored. The modified catalyst was then washed with distilled water (2 x 40 cm^3), methanol (30 cm^3) and finally the reaction solvent, butan-1-ol (20 cm^3). The modified catalyst sample was then dried in vacuo.

Section 3.2.2 Catalyst Activation.

Modification of Raney Nickel by Tartaric Acid / Sodium Bromide.

(R,R)-+-tartaric acid (1g, 6.7 x 10^{-3} mol) and sodium bromide (10g, 9.07 x 10^{-3} mol) were dissolved in distilled water (100 cm^3) and the pH of the solution adjusted from 1.3 to pH 3.2, with 1 mol dm^{-3} sodium hydroxide solution.

The modifying solution was heated to 373 K in an oil bath and freshly prepared Raney nickel added; the solution was maintained at this temperature for 1 hour with continual stirring. After this time the modifying solution was decanted and the catalyst was washed with distilled water (30 cm^3), methanol (25 cm^3) and finally with butan-1-ol (25 cm^3).

The modified Raney nickel was then transfered under butan-1-ol to the reaction vessel described in Section 3.3.2.

Section 3.2.3

Atomic Absorption Analysis of Modifying Solutions For The Presence of Nickel (II).

After the modification of catalyst samples the modifying solutions, upon inspection, were found to exhibit a green coloration indicative of the presence of

nickel (II) ions. The nickel contents of modifying solutions were determined by atomic absorption spectrophotometry using the instrument and technique described in Section 3.1.2, correcting the calibration curve for the presence of tartaric acid.

Section 3.3.1 Catalytic Studies.

The Apparatus: Catalytic Reactor I.

Initial catalytic studies were carried out using the catalytic reactor shown in Figure 3.3.1a which was constructed in Pyrex glass from a design described by Hoek and Sachtler[68].

The Ni/SiO_2 catalyst sample was dispersed on the glass sinter (porosity 4) and reduced in a flow of hydrogen gas through tap T1 and out through tap T3 to a bubble flow meter, which was used to measure the hydrogen flow rate. The catalyst was heated at a variable rate with an external furnace of the type described in Section 3.3.3

The solutions used to modify and wash the reduced catalyst, and the reaction mixture were admitted to the catalytic reactor via tap T4 from a reservoir which was connected to a high vacuum glass line (described in Section 3.3.4), used to de-gas the liquids before contact with the freshly reduced catalyst.

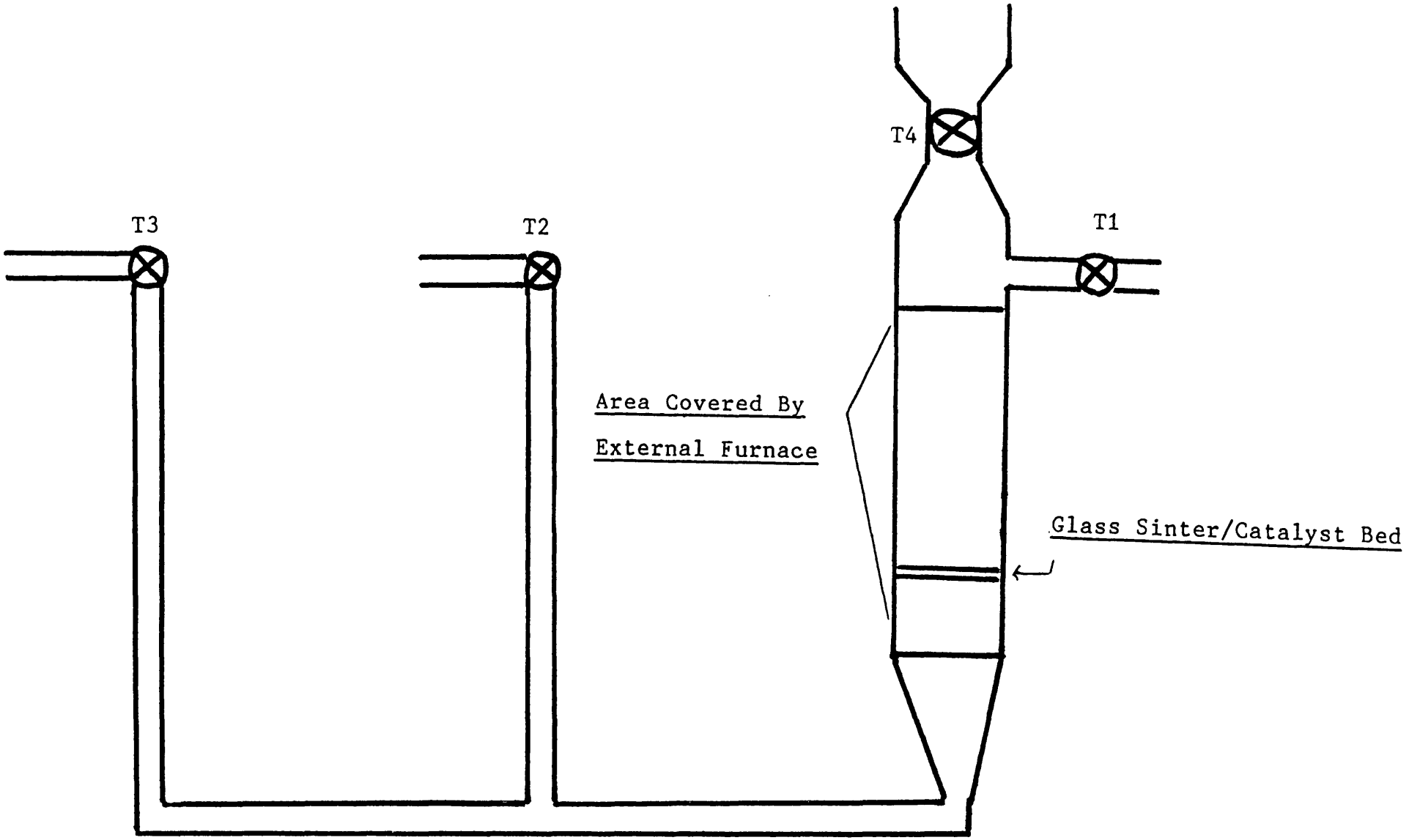


Figure 3.3.1a

Catalytic Reactor I

In the case of Reactor I a flow of nitrogen gas was admitted via tap T3 and out through tap T1 during modification, constantly agitating the catalyst sample in the solution.

For the atmospheric pressure hydrogenation of MAA, the Reactor I was connected to the high vacuum glass line and the reaction allowed to proceed with periodic mechanical shaking of the catalyst / reaction mixture suspension.

Both the modifying and product solutions were removed from Reactor I via tap T2 and collected in a cold trap cooled to liquid nitrogen temperature.

The taps T1...T4 of Reactor I were Youngs Double 'O' ring taps.

Section 3.3.2 Catalytic Studies.

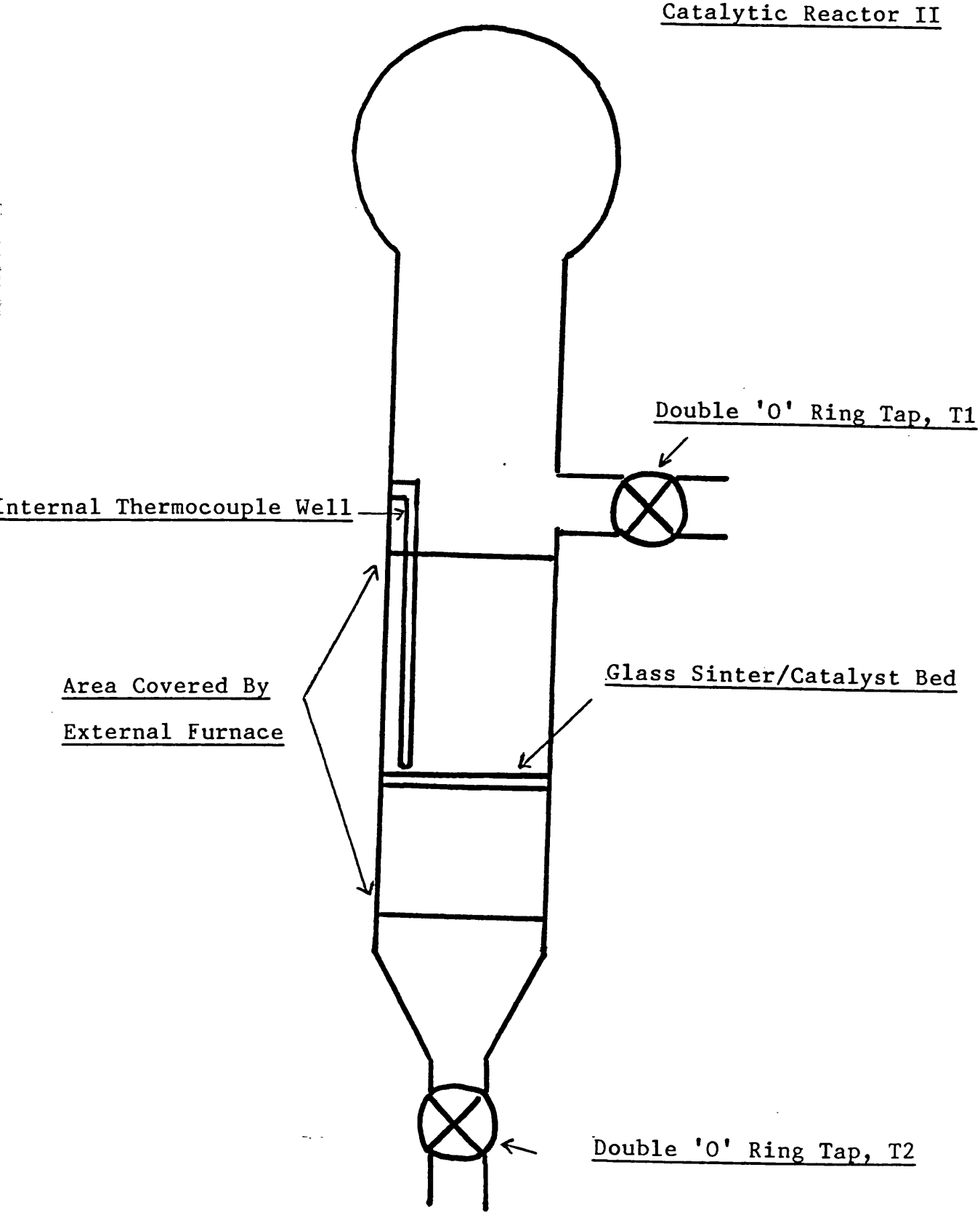
The Apparatus: Catalytic Reactor II.

The Ni/SiO_2 catalyst samples were also modified in situ in the reactor shown in Figure 3.3.2a, followed by the atmospheric hydrogenation of MAA.

The calcination and reduction steps were carried out with the catalyst sample dispersed on the glass sinter (Porosity 4) of the Reactor II. The catalyst was heated at a variable rate using an external furnace of the type described in Section 3.3.3. The temperature of the catalyst bed was measured by a thermocouple placed in

Figure 3.3.2a

Catalytic Reactor II



the internal well of the Reactor II and recorded by a Comark thermometer.

Catalyst samples were calcined prior to reduction by heating under vacuum with tap T2 of the Reactor II connected by flexible tubing to tap Ta of the high vacuum glass line (Section 3.3.4)

The catalyst samples were reduced in a 150 cm^3 min^{-1} flow of hydrogen gas, admitted to the Reactor II via tap T1, to pass through the catalyst bed and exit via tap T2 to a bubble flow meter which measured the flow of gas.

The solutions used to modify and wash the catalyst , and the reaction mixture to be hydrogenated, were introduced from a glass reservoir (Figure 3.3.2b) connected to Reactor II via tap T1. The top of the glass reservoir was connected to tap Tb of the high vacuum glass line to facilitate a thorough de-gassing of liquids before to admission to Reactor II and contact with the freshly reduced catalyst sample.

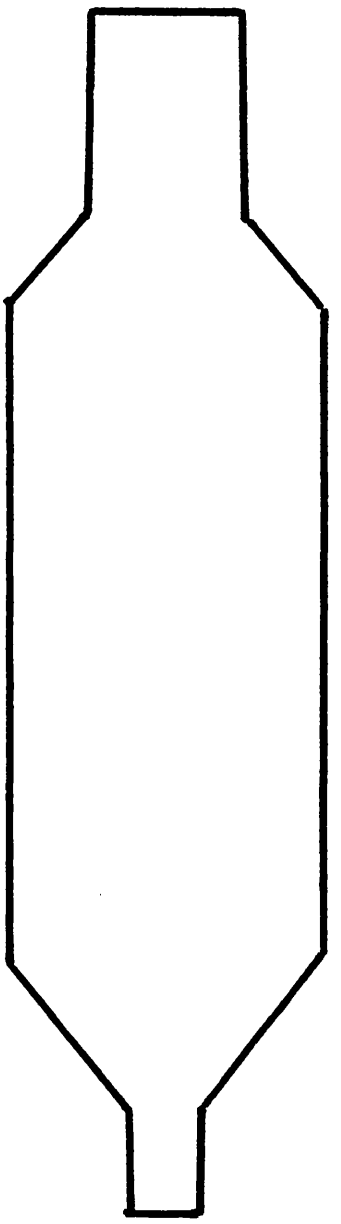
The catalyst / solvent suspensions were vigorously stirred in the round bottomed end of Reactor II using a magnetic stirrer and bar. The temperatures of catalyst modification and MAA reduction were achieved by placing the round bottomed end of the reactor in an oil bath.

Solutions were removed via tap T2 to a cold trap cooled to liquid nitrogen temperature. The catalyst

Figure 3.3.2b

Glass Reservoir

To High Vacuum Glass Line



To Tap T1 Of Catalytic Reactor II

ineffect, "filtered" from the solutions by the glass sinter of Reactor II.

The taps T1 and T2 of Reactor II were Youngs Double 'O' ring taps.

Section 3.3.3 Catalytic Studies. The External Furnace.

The furnace used during thermal activation of the catalyst was constructed by wrapping the required area of the catalytic reactor in a sheet of mica coated glass fibre. This was secured with tinned copper wire at the top and bottom which also served as the terminals for the electricity supply. Between these terminals [the figures following are for the furnace of Reactor II] resistance wire (29.7 ohms m^{-1}) was wound round the circumferance (0.15 m) and the distance from one terminal to the other was 0.20 m. The resistance wire, wound in 23 roughly equidistant turns gave a total resistance of 102.3 ohms. The resistance wire was then covered by another sheet of mica coated glass fibre.

The terminals were connected to a Variac voltage controller via ceramic connecting blocks. The temperature of the furnace was increased by increasing the voltage output from the Variac. An output voltage of 140 volts was sufficient to ensure a temperature of

723 K. At this voltage and the known resistance of the furnace wire, the current (I), from Ohms law $I = \frac{V}{R}$ is 1.4 amps.

Section 3.3.4 Catalytic Studies.

1. The High Vacuum Glass Line / 2. Atmospheric Pressure Liquid Phase Hydrogenation System.

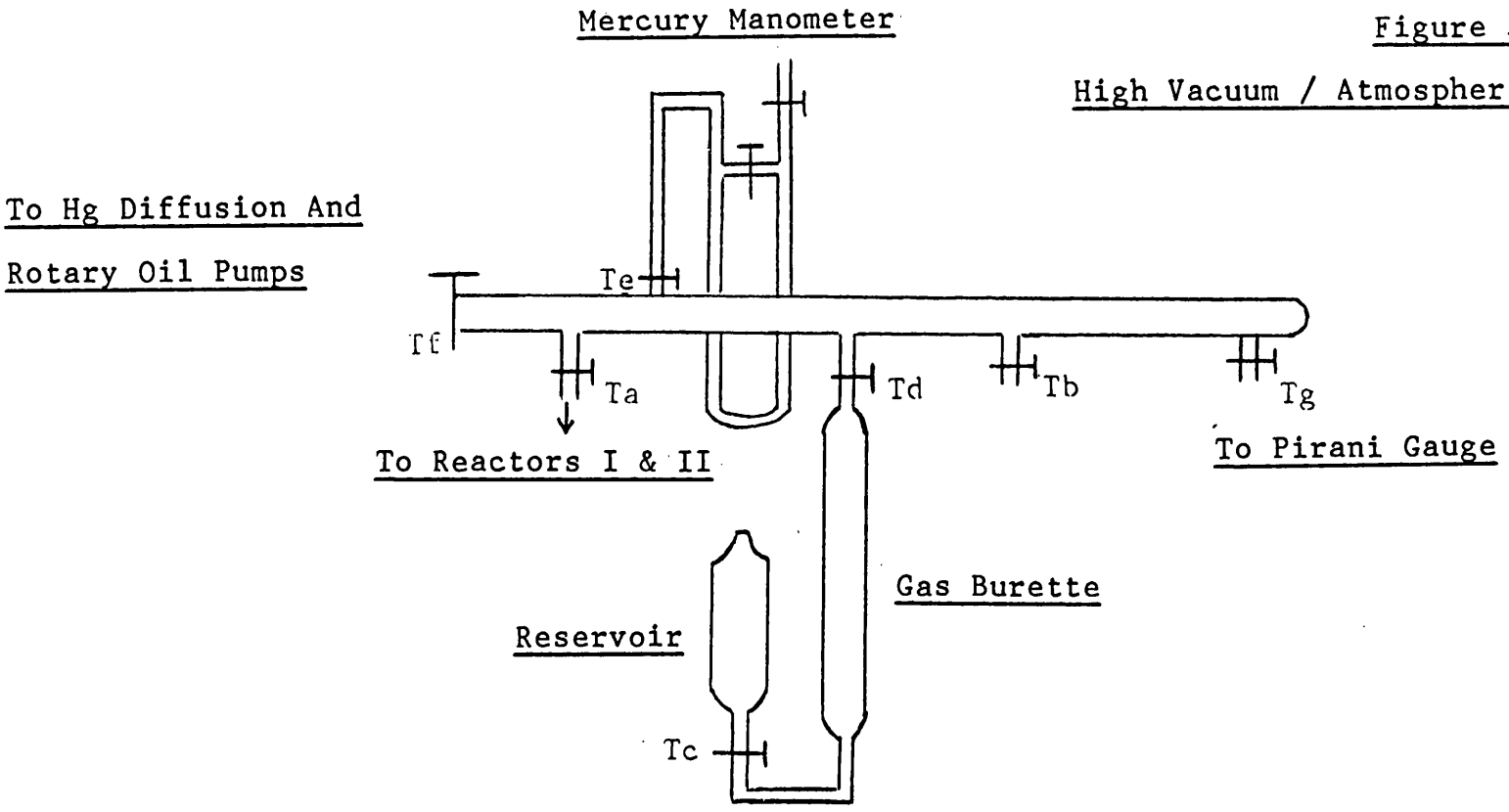
The glass line shown in Figure 3.3.4a was used in conjunction with Reactors I & II for the stages of catalytic study that required a vacuum (in vacuo pre-treatment of catalysts, liquid degassing and removal) and for atmospheric hydrogenations of MAA.

Pressures of 10^{-4} torr, measured by a Pirani gauge, connected to the 4 mm glass tap Tg of the high vacuum glass line, were achieved using a water cooled mercury diffusion pump in series with two cold traps cooled to liquid nitrogen temperature and a rotary oil pump. This part of the system could be isolated from the main manifold by a 10 mm tap Tf during atmospheric hydrogenation reactions.

This system was connected to Reactors I & II via tap Ta and flexible tubing. Hydrogen gas was admitted to this system through taps T1 of the reactors and the admitted pressure was measured by a two limbed mercury manometer attached to the main manifold by a 4 mm glass tap Te.

Figure 3.3.4a

High Vacuum / Atmospheric Pressure Glass Line



A methanol filled glass reservoir was attached with flexible tubing to a 500 cm^3 gas burette. The flow of methanol between reservoir and burette was controlled by a 4 mm tap Tc, fitted to the reservoir. Admission of hydrogen gas to the burette was possible through a 4 mm tap Td.

A 4 mm tap Tb was connected by flexible tubing to a B 19 'Quickfit' socket which was used for attachment to the cones of the reservoirs of Reactors I & II used in the de-gassing and admission of liquids to the reactors.

All cone and socket connections and 4 mm glass taps were lubricated with Apiezon 'N' grease.

Section 3.3.5 Catalytic Studies.

The Procedure For Atmospheric Pressure Hydrogenation

A solution of MAA (10 g, 8.62×10^{-3} mol) in butanol was de-gassed and admitted to the Reactor containing the freshly modified Ni/SiO_2 catalyst as described in Sections 3.3.1 & 2. In experiments involving Raney Ni the reaction mixture was added to the freshly prepared modified catalyst, which was stored under 20 cm^3 of butan-1-ol. In this section the procedure for hydrogenation is described with reference to Reactor II.

The reaction mixture and the catalyst in the round bottomed end of the reactor were immersed in an oil bath

pre-heated to the reaction temperature (343 K). The gas burette was then evacuated via tap Td. Hydrogen gas was admitted to the system through Reactor II (via taps T1 to T2) and tap Ta of the high vacuum glass line (Section 3.3.4) to a pressure of 800 torr as indicated by the mercury manometer, this hydrogen was removed immediately afterwards by opening tap Tf. This procedure was repeated three times to ensure that all air was purged from the system. After the fifth admission of hydrogen, pressure was reduced from 800 to 760 torr in the following way :-

(i) The glass reservoir, which was open to the atmosphere was raised to a position such that the methanol level was the same as in the gas burette.

(ii) Tap Tc was opened to allow methanol to flow from the burette into the reservoir to enable the methanol levels to remain equal.

The magnetic stirrer was switched on for the duration of the reaction, ensuring an efficient mixing of the reacting species.

At maximum conversion (ca. 90 % MHB), time typically in the range of 40 to 60 hours, the reaction mixture was collected in a liquid nitrogen cooled cold trap.

Section 3.3.6 Catalytic Studies.

An Alternative Procedure For The Hydrogenation of MAA.

The procedure described in the previous section had a limitation with regard to the contact of the reacting species and the catalyst. This was indicated by the irreducibility in the overall levels of hydrogenation and enantiodifferentiation[48], in static atmospheric hydrogenation reactions. This limitation is that the catalyst and MAA in butan-1-ol are agitated below an atmosphere of hydrogen and diffusion constraints reduce the concentration of hydrogen at the catalyst surface.

To over come this difficulty a system was developed to ensure that hydrogen was in close contact with the active surface by Keane and Webb[123] which improved reproducibility of results. This method involved direct bubbling of hydrogen gas through the MAA, butan-1-ol/ catalyst suspension at a fixed rate and with constant agitation of the suspension.

For the purposes of this study of MAA hydrogenation, a side-arm was added to the round bottomed end of Reactor II through which hydrogen gas was bubbled directly into the MAA, butan-1-ol/ catalyst suspension at a flow rate of 30 cm^3 min^{-1} with constant stirring of the mixture. All other aspects of catalyst preparation, handling, and MAA hydrogenation were as before.

Section 3.4.1 Product Analysis. Gas Chromatography (G.C.).

Resolution of the reaction mixture into the butan-1-ol, MAA and MHB components was achieved using a 10' long, ¼" o.d. stainless steel column, packed with a 15% w/w dispersion of UCON fluid supported on Chromosorb W.

Chromatographic separation was carried out using a Pye Unicam G.C. instrument fitted with a flame ionisation detector (F.I.D.).

A typical chromatogram of a test mixture of MAA, MHB and butan-1-ol is shown in Figure 3.4.1a. The conditions for resolution of the reaction mixture were as follows:-

Carrier Gas= Nitrogen, Flow-rate= 90 cm^3 min^{-1}

Detector Oven Temperature= 423 K

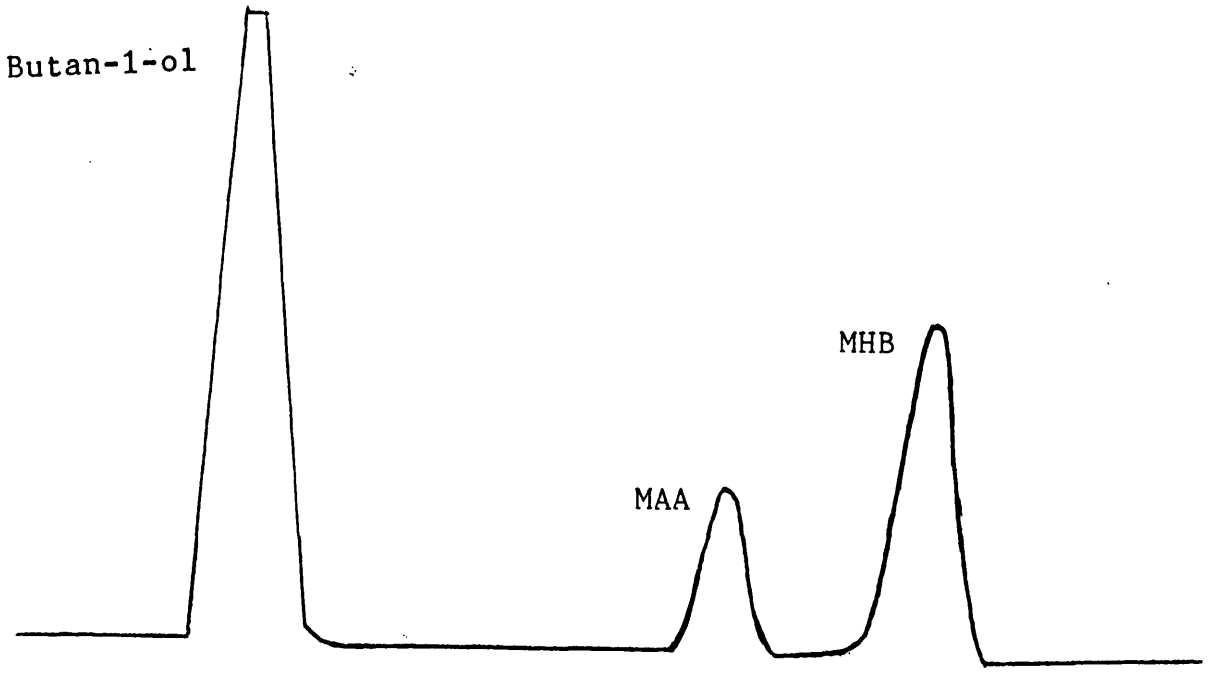
Column Temperature= 398 K

Prior to analysis of reaction mixtures the F.I.D was calibrated to determine the Response factors (R) of MAA and MHB, as follows;

For a substance x, Rx can be defined as the number of moles of x per unit area of chromatogram peak produced by a known volume of pure x. The calibration was achieved by obtaining separate chromatograms of 1 micro litre samples of pure MAA and MHB and measuring the

Figure 3.4.1a

Gas Chromatogram Of MAA / MHB / Butan-1-ol



area of the resultant peaks. Over a series of ten 1 micro litre injections of MAA and MHB the error involved in performing gas chromatographic analysis was found to be +/- 1%.

Values for the response factor Rx were calculated in the following way:-

$$Rx = \left(\frac{\text{Peak Area Of x}}{\text{No. moles of x (1}\mu\text{l)}}\right)^{-1} \left(\text{area mol}^{-1}\right)^{-1}$$

(No. = number of)

Typical retention times and response factors are shown in Table 3.4.1.

Table 3.4.1

	MAA	MHB
RETENTION (min)	70	85
RESPONSE FACTOR $(\text{area mol}^{-1})^{-1}$	1.75×10^{-5}	9.68×10^{-6}

Multiplication of the peak areas, from the chromatograms of the reaction mixtures, by the appropriate response factor gives the number of moles present of MAA and MHB.

The percentage conversion, Y, of MAA to MHB can be calculated using the G.C. analysis and assuming that

$$1 \text{ mole MAA} \xrightarrow{H_2} 1 \text{ mole MHB}$$

i.e. a 1:1 mole relationship. The percentage conversion

can be represented as

$$Y_{\%} = \frac{\text{No. moles MAA hydrogenated to MHB}}{\text{No. moles MAA initially present}} \times 100$$

The numerator in this equation is the number of moles of MHB, n_{MHB}, determined by G.C.

Since the MAA present initially was either hydrogenated to MHB ($=n_{MHB}$) or remained in the reaction mixture and determined by G.C. ($=n_{MAA}$) the denominator simplified to $n_{MAA} + n_{MHB}$.

Thus the percentage conversion cou ld be expressed as

$$Y_{\%} = \frac{n_{MHB}}{n_{MAA} + n_{MHB}} \times 100$$

The percentage conversion, gave the total concentration of MHB in the reaction mixture (C_{tot}) and this was used in conjunction with Polarimetric measurements (Section 3.4.3) to determine the enantiomeric excess of the reaction mixture.

Section 3.4.2 Product Analysis.

High Performance Liquid Chromatography.

Liquid chromatography (H.P.L.C., Spectra Physics) was also used to calculate the extent of hydrogenation of MAA to MHB. The separations were achieved on a Pirkle type 1A 5μ reversible column (250×4.6 mm) with a 10%

propan-2-ol : 90% hexane (by volume) mixture as the eluant. All the H.P.L.C. grade solvents were supplied by Rathburn Chemicals and were thoroughly purged with helium prior to use.

The presence of MAA and MHB in the product mixture was determined by a U.V. detector (λ = 254 nm) in conjunction with a Pye Unicam PU4810 integrator. A typical chromatogram showing MAA and MHB separation using this system is shown in Figure 3.4.2a.

The area of each peak cannot be directly related to the amount of each component because detection is by U.V. absorbance, and the area of the peak relates to this. From the Beer-Lambert law

$$A = c \varepsilon_o 1$$

where A is the absorbance, c is the concentration of a component and ε_o is the extinction coefficient of it and 1 is the path length of the cell.

As 1 is the same for both MAA and MHB the area measured for each component will depend on its concentration and its extinction coefficient.

The system was therefore calibrated using MAA / MHB mixtures of known composition. A 22 point calibration curve was constructed and fitted to the equation:-

$$Y = 0.4877\ X + 2.61 \times 10^{-2}$$

where Y = mole% MHB and X = log (Area MHB).

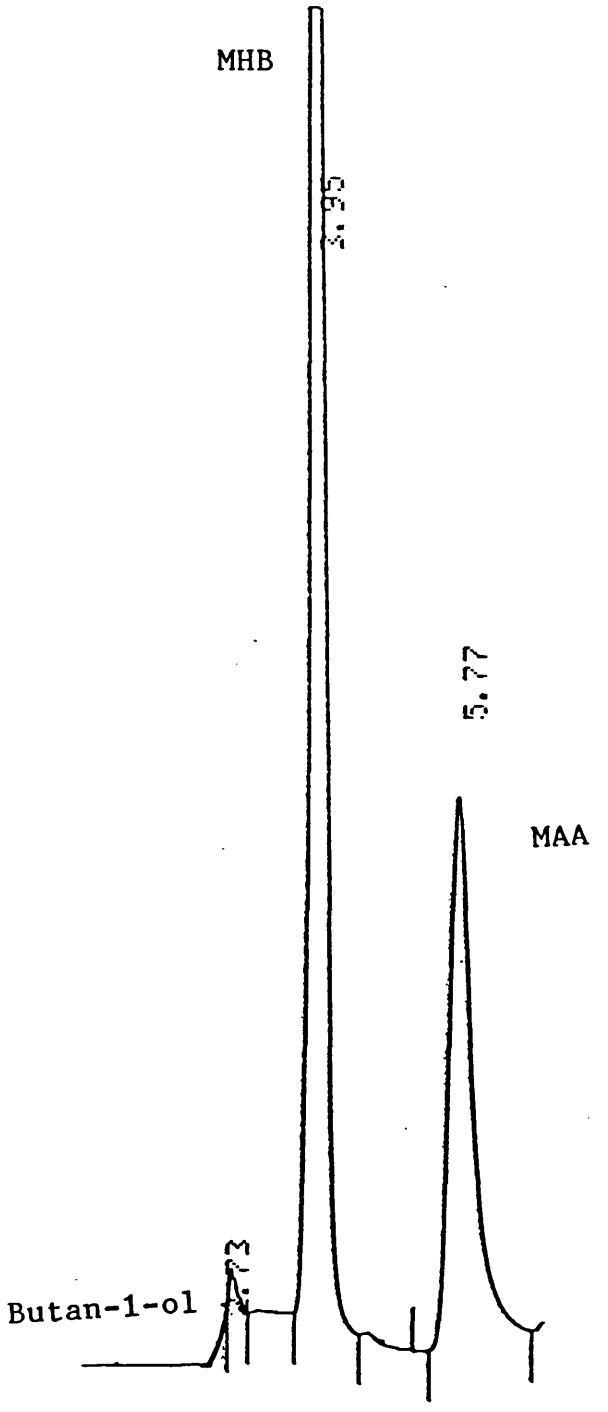


Figure 3.4.2a

High Performance Liquid Chromatogram Of MAA / MHB / Butan-1-ol

From this relationship the concentration of MHB could be be determined (within +/- 1%).

Section 3.4.3 Product Analysis. Polarimetry And The Calculation of Enantiomeric Excess.

Polarimetric measurements of reaction mixtures were made using an AA-10 automatic digital polarimeter (Optical Activity Ltd.).

All measurements were made at 293 K using the D-line in the sodium emission spectrum (wavelength = 589 nm) as the monochromatic light source. The polarimeter cell used throughout was of capacity 1 cm^3 and length 1 dm.

The procedure was as follows:-
The digital display was set to zero with the cell filled with butan-1-ol. The cell was then washed with acetone and thoroughly dried. A sample of the reaction mixture was carefully added to the cell and the measured angle of rotation, α, noted.

From this measurement and the chromatographically measured total concentration of MHB, the enantiomeric excess (equation 3.4.3b) was calculated.

The specific rotation $[\alpha]^{293K}_{589nm}$, which is -22.95 for pure (R) MHB is related to the measured angle of rotation

of the reaction mixture by the equation:-

$$[\alpha]^{293\ K}_{589\ nm} = \frac{\alpha}{1 \times c'_R} \qquad (3.4.3a)$$

where 1 is the pathlength of the polarimeter cell, in this case 1 dm. The value of c'_R is calculated from this equation and is defined as $c' = (c_R - c_S)$ where c_R and c_S is the concentration [mg cm^{-3}] of each respective enantiomer in the reaction mixture. When the value of c'_R is positive, there is an excess of the R enantiomer of MHB, when negative there is an excess of (S)-MHB. [The use of (R,R)-tartaric acid modified catalysts in the hydrogenation of MAA give excesses of (R)-MHB].

The enantiomeric excess (e.e.) of a reaction is defined as:-

$$\text{e.e.}_{\%} = \frac{(c_R - c_S)}{(c_R + c_S)} \times 100 \qquad (3.4.3b)$$

The numerator, $(c_R - c_S)$, is c'_R calculated from equation 3.4.3a. The denominator is the total concentration of MHB in 1 cm^3, c'_{TOT} calculated from chromatographic analysis (Sections 3.4.1 & 2) thus

equation 3.4.3b simplifies to:-

$$e.e._{\%} = \frac{c'_R}{c'_{TOT}} \times 100 \quad (3.4.3c)$$

CHAPTER FOUR

RESULTS

Section 4.1 Catalyst Activation.

Reduction of Ni/SiO_2 Catalyst Precursors.

The initial stage in the procedure for establishing a Ni/SiO_2 catalyst with enantiodifferentiating ability is ideally the complete reduction of the nickel (II) salt to nickel (0). As a guide to the reduction behaviour of the Ni/SiO_2 (I) catalyst precursor(Section 3.1.2), the Temperature Programmed Reduction (T.P.R.) profile of the unreduced catalyst was determined. T.P.R. experiments measure the hydrogen uptake of a known weight of catalyst sample as a function of increasing temperature. Full details of T.P.R. experiments are described elsewhere[130] but the conditions used for Ni/SiO_2 (I) catalyst precursor were as follows:-

Weight of hydrated Ni/SiO_2 (I) : ca. 0.2g

Initial Temperature : 293K Final Temperature : 1073K

Temperature Ramp Rate : 5 K min^{-1}

Reducing Gas : 6% (v/v) H_2/N_2

Gas Flow Rate : 25 cm^3 min^{-1}

The T.P.R. profile recorded using these conditions is shown in Figure 4.1a. The temperatures corresponding to a maximum of hydrogen uptake (T_{max} values) are given in Table 4.1a. Based on these findings, initial conditions for catalyst reduction were determined (Section 4.2).

Figure 4.1a The T.P.R. Profile For Ni/SiO_2 (I) Under The Conditions Stated In Section 4.1.

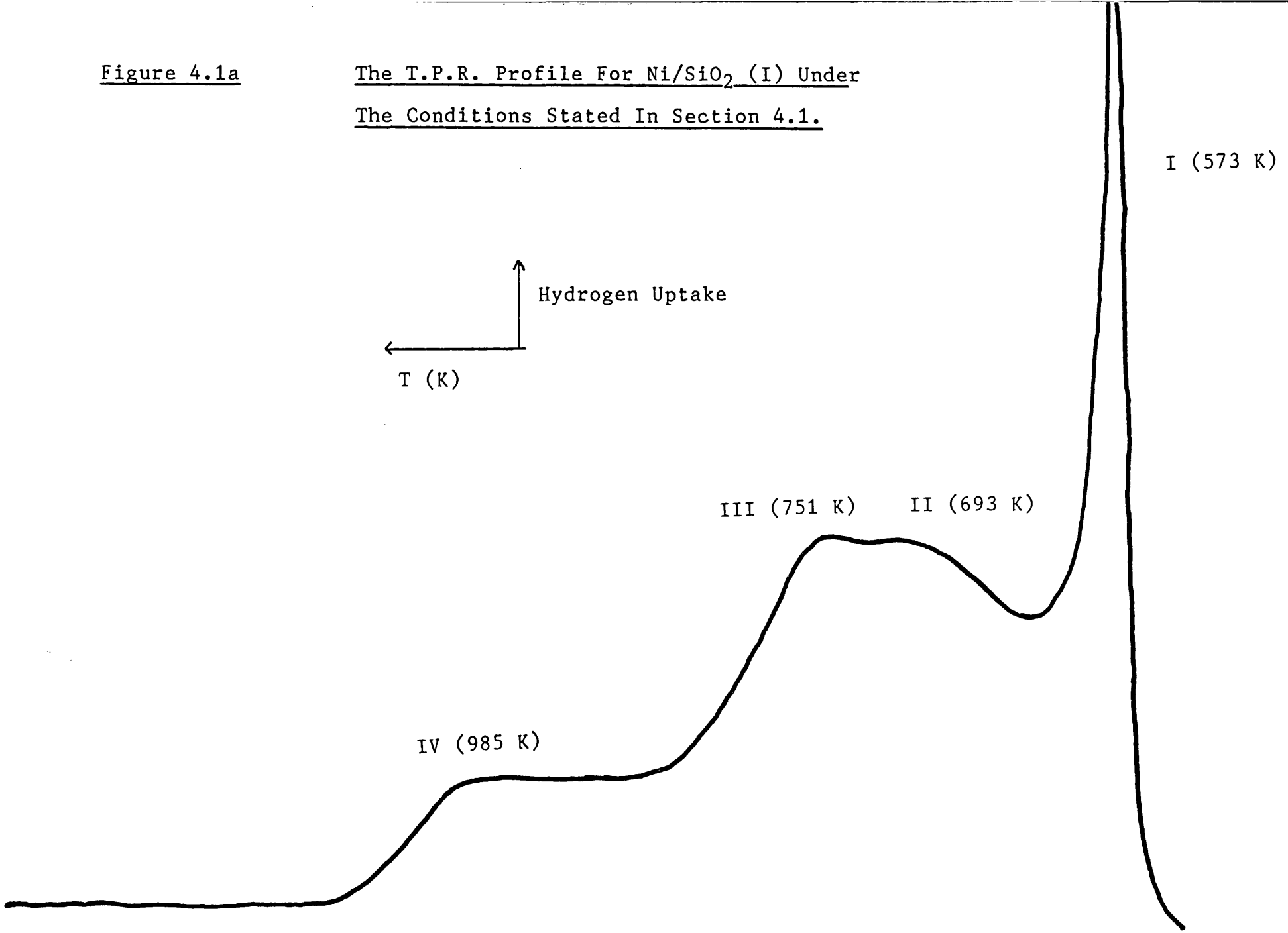


Table 4.1a

T_{max}	Temperature K
I	573
II	693
III	751
IV	985

Section 4.2 Initial Catalyst Activation Conditions And Catalytic Studies.

The initial part of the present work was on the activation of Ni/SiO_2 (I) for use in atmospheric pressure hydrogenation reactions using Catalytic Reactor I (Section 3.3.1) in conjunction with the high vacuum glass line (Section 3.3.4).

A sample of the catalyst precursor Ni/SiO_2 (I) (1g) was reduced at 573 K in a 1 cm^3 min^{-1} flow of pure hydrogen gas and maintained at this temperature for 6 hours. The flow of gas used was a fraction of that used in the T.P.R. experiment as pure hydrogen gas rather than diluted hydrogen was used. The temperature of reduction corresponded to T_{max} I of the T.P.R. profile; the peak of largest hydrogen uptake. It was assumed that the prolonged treatment at this temperature would result in the complete reduction of the nickel (II) to nickel metal.

As the temperature of the catalyst bed was increased linearly with time to 573 K, the gaseous products of reduction i.e. H_2O and NO_x were observed above the catalyst bed in the area of Reactor I not covered by the external furnace. The water vapour condensed on the reactor walls above the furnace area and was still present when brown NO_x fumes became visible as the reduction temperature exceeded 473 K.

After reduction the catalyst was not uniform in appearance, in that the particles ranged in colour from black through grey to white.

After the reduction step, the "activated" catalyst was modified using similar conditions and procedure as optimised for Raney Ni[22] and which are described fully in Section 3.2.2. When the modifying solution was isolated from the catalyst it exhibited deep coloration, indicative of the presence of nickel (II) ions. The catalyst sample itself was green/white in appearance.

The catalyst sample, thus modified, was then used in the atmospheric pressure hydrogenation of MAA (5.5g, 4.7×10^{-2} mol) in butan-1-ol (50 cm^3) to MHB, reaction time ($t_{reaction}$)= 24 hours. Gas chromatographic analysis of the product mixure showed no conversion of MAA to MHB.

Repeating these conditions of catalyst activation

on other samples of Ni/SiO_2 (I) gave similar results, the samples being inactive as catalysts in hydrogenation reactions of MAA.

Section 4.3.1. Catalyst Activation. Improved Conditions of Catalyst Precursor Reduction.

The presence of Ni(II) ions in the modifying solution after the two-step activation of Ni/SiO_2 (I) were thought to be due to unreduced ions being washed directly from the catalyst surface. For this reason, three alternative reduction procedures were tested in sequence:-

(a) A sample of Ni/SiO_2 (I) (1g) was calcined by heating to 573 K in a 25 cm^3 min^{-1} flow of air, and then reduced by heating to 673 K in a 3 cm^3 min^{-1} flow of hydrogen gas, the final temperature being maintained for 16 hours.

(b) It has been suggested[131] the extent of nickel reduction could be increased by including a more active metal in the catalyst precursor. For this reason a (10% Ni, 0.1% Pt) silica (w/w) was prepared by impregnation (Section 3.1.1.b). A sample of this catalyst (1g) was reduced according to method (a).

(c) A new set of reduction conditions, as described in Section 3.2, based on criteria for improved reduction of nickel/silica catalysts discussed by

Martin et al[125].

Each of these reduction methods still yielded no measurable level of hydrogenation and consequently no enantiodifferentiation, after modification using the conditions developed for Raney nickel (Section 3.2.2). Again the modifying solutions had the green coloration of nickel(II).

Section 4.3.2 Catalyst Activation. Modification of Ni/SiO_2 (I) by Tartaric Acid/NaBr.

An alternative source of Ni(II) ions in the modifying solution may be the corrosion of nickel metal during the modification procedure. This phenomenon is not an unknown feature of catalyst modification, as the adsorption of tartaric acid on Raney Ni catalysts had been referred to as "Corrosive Chemisorption"[68]. It was not suggested, however, that this process could completely remove all hydrogenating and thus enantiodifferentiating ability from the Raney nickel catalysts.

To observe if catalyst corrosion could be limited it was decided to modify a sample of the reduced Ni/SiO_2 I with a more dilute tartaric acid (T.A.) solution i.e. [T.A.]= 6.67×10^{-3} mol dm^{-3}, rather than 6.67×10^{-2} mol dm^{-3}(= 1g T.A.). The remaining variables were as before;

namely:-

Volume Of Solution: 100 cm^3

Concentration Of NaBr: 0.97 mol dm^{-3} (=10g NaBr)

pH Of T.A./NaBr solution: 3.2 (Adjusted with $NaOH_{aq}$)

Modification Temperature (T_{mod}): 373 K

Modification Time (t_{mod}): 1 hour

The effect of this alteration in the modification step was to induce slight hydrogenation and enantioselective ability in the catalyst; for example the conversion of MAA to MHB ranged from 14% ($t_{reaction}$ = 16 hours) to 25% ($t_{reaction}$ = 30 hours) with an enantiomeric excess of 8% and 5% respectively.

Although these conversions and enantioselectivities were low, they did show that reducing the concentration of tartaric acid had a beneficial effect. Thus the results clearly show that the optimum modification conditions developed for Raney Ni are not applicable for the modification of Ni/SiO_2 catalysts.

At this stage, it was decided to further investigate the role of the modification step of catalyst activation having decided that the best conditions for catalyst reduction were those outlined by Martin et al.[125], which are described in Section 3.2.

Section 4.4.1 Catalytic Studies. Catalytic Reactors I/II.

During the initial work on catalyst activation and MAA hydrogenation, it became apparent that Reactor I (Section 3.3.1) was unsuitable. The awkward shape of this reactor made it difficult to manipulate when removing modifying and reaction solutions and mitigated against the successful and speedy washing of the modified catalyst (and reactor) prior to catalytic studies. More importantly, the nature of the reactor did not allow for constant agitation of the catalyst/ reaction mixture suspension, which would certainly have contributed to the low levels of MAA hydrogenation. During the hydrogenation of MAA it was noted that there was a loss of 5-10 cm^3 of the reaction mixture through the porous sinter when $t_{reaction}$ = 16 hours.

For these reasons, catalytic Reactor II (Section 3.3. 2) was designed. This proved to be a more efficient system as was demonstrated in the subsequent catalytic activation and MAA hydrogenation studies.

The reproducibility of MAA hydrogenation results has been reported to be improved[48] in non-static hydrogenation conditions. For this reason Reactor II was adapted to be suitable for non-static hydrogenations (the adaptation and procedure are described in Section

3.3.6). All further hydrogenation reactions were by this method rather than the static atmospheric pressure hydrogenation procedure (Section 3.3.5).

Section 4.5.1 The Effect of Tartaric Acid Concentration on The Modification of Ni/SiO_2 (I).

The effect of altering the concentration of (R,R)-+-T.A. during the modification of samples Ni/SiO_2 (I) in terms of nickel corrosion and the hydrogenation and enantiodifferentiating ability of the catalyst was examined. The extent of nickel corrosion was determined by atomic absorption spectrophotometry, by analysis of the post-modification solutions (Section 3.2.3).

The remaining modification parameters were as listed in Section 3.2.2 with the exception that the concentration of sodium bromide was lowered to 0.19 mol dm^{-3}. The relationship between [T.A.] and the extent of nickel leaching is illustrated in Figure 4.5.1a.

The amount of nickel corroded when the concentration of T.A. is 6.67×10^{-2} mol dm^{-3} is equivalent to a loss of 60% of the nickel content of the original sample of Ni/SiO_2 (I) (1g).

The effect of [T.A.] on the hydrogenating and the enantiodifferentiating ability of the catalyst samples is shown in Table 4.5.1a.

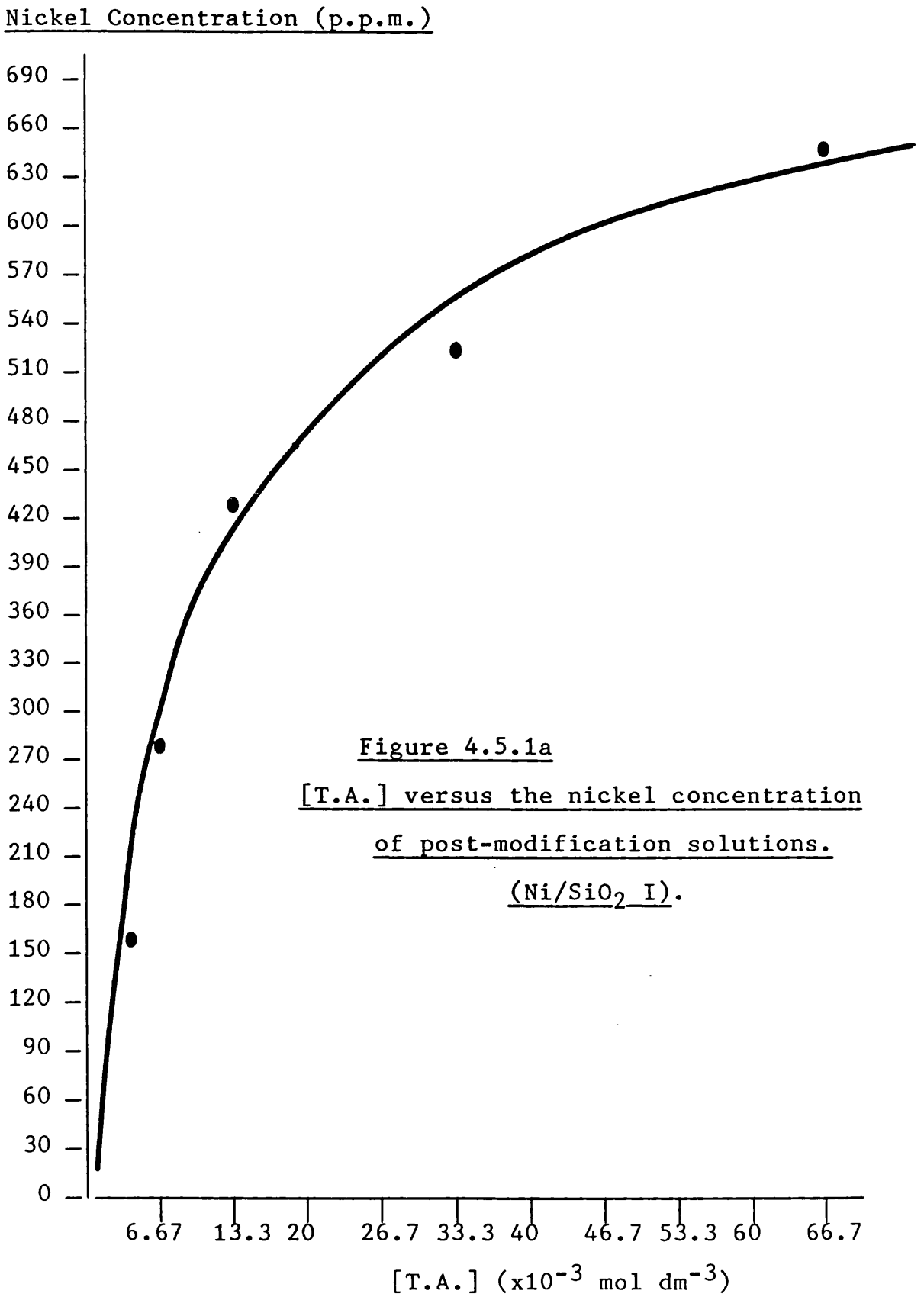


Figure 4.5.1a

[T.A.] versus the nickel concentration of post-modification solutions. (Ni/SiO_2 I).

Table 4.5.1a*

[T.A.] mol dm^{-3}	mole% MHB[a]	enantiomeric excess%[b]
3.33×10^{-3}	92	14
6.67×10^{-3}	90	29
1.33×10^{-2}	90	13
6.67×10^{-2}	0	0

*Hydrogenation Conditions: 10g MAA/1g Ni/SiO_2 in 50 cm^3 butan-1-ol. $t_{reaction}$= 60 hours, $T_{reaction}$ = 343 K

a Calculated from H.P.L.C. analysis.

b Calculated from H.P.L.C. analysis and Polarimetry.

As a control experiment, a reduced sample of Ni/SiO_2 I (1g) was stirred in an aqueous solution of HCl(pH=3.2) at 373 K for 1 hour. The catalyst was filtered from the solution which was then analysed by Atomic Absorption; the nickel content was found to be 65 p.p.m.

To measure the extent of nickel leeching caused by contact of T.A. with unreduced nickel (II) ions after catalyst reduction, the following experiment was carried out. A sample of Ni/SiO_2 (I) was heated in vacuo to 723 K at 10 K min^{-1} and this temperature maintained for 1 hour. This calcined sample was stirred in a solution of T.A.(6.67×10^{-3} mol dm^{-3}),NaBr(0.19 mol dm^{-3}),pH = 3.2, for 1 hour at 373 K, then filtered from

the solution which was then analysed for nickel(II), again by atomic absorption; the nickel content was found to be 9 p.p.m.

These two experiments show that the original acidity of the solutions or the presence of unreduced nickel prior to modification accounts for only a fraction of nickel leached during catalyst modification: 65 & 9 p.p.m. compared to 270 p.p.m Ni when a reduced sample of Ni/SiO_2 (I) is modified in a solution of [T.A.]=6.67 x 10^{-3} mol dm^{-3}.

To further investigate the modification step of catalyst activation, the T.A. concentration was kept constant at 6.67 x 10^{-3} mol dm^{-3}, while other parameters were systematically varied in the following studies.

Section 4.5.2

The Effect of Sodium Bromide.

The effect of NaBr, in the modifying solution, on nickel corrosion, MAA hydrogenation activity and enantiodifferentiating ability, was determined by modifying one sample of Ni/SiO_2 (I) in the presence of NaBr (0.19 mol dm^{-3}) and another in the absence of NaBr. The result of each case is shown in Table 4.5.2a. The conditions of hydrogenation were as follows:- 10g MAA/1g Ni/SiO_2 (I), 50 cm^3 butan-1-ol and $t_{reaction}$ = 60 hours.

Table 4.5.2a

[T.A.] mol dm^{-3}	[NaBr]	Ni leached[a] p.p.m.	mole% MHB	e.e.%
6.67×10^{-3}	0.19	270	90	29
6.67×10^{-3}	-	266	93	25

a 'Ni leached' is the Ni concentration of the solution after modification.

The results show that there is an increase in e.e. with NaBr addition accompanied with a slight decrease in activity, as determined by the mole % yield of MHB in the product mixture.

Section 4.5.3

The Effect of Modification Temperature(T_{mod}).

To determine the effect of altering the temperature of modification(T_{mod}) on nickel leeching and catalyst performance, samples of reduced Ni/SiO_2 (I) (1g) were modified at different temperatures. The constants of modification in these experiments were as shown in Table 4.5.3a:-

Table 4.5.3a

[T.A.] mol dm^{-3}	[NaBr] mol dm^{-3}	Volume Of Solution(cm^3)	pH	t_{mod} hours
6.67×10^{-3}	0.19	100	3.2	1

The modified catalysts were used to hydrogenate 10g MAA in 50 cm^3 butan-1-ol. The data relating to nickel leaching during modification and the hydrogenation activity of the catalysts are shown in Table 4.5.3b. The relationship between T_{mod} and nickel leaching is illustrated in Figure 4.5.3a and between T_{mod} and enantiomeric excess in Figure 4.5.3b.

Table 4.5.3b

Ni/SiO_2 (I) 1g	T_{mod}(K)	Ni leached p.p.m.	mole%MHB	e.e.%
YES	273	50	94	23
YES	293	72	91	21
YES	333	220	93	32
YES	373	270	90	29

Thus for the Ni/SiO_2 (I) catalyst the optimum value of T_{mod} (in terms of enantiodifferentiating ability) is not 373 K, the optimum value for Raney Ni modification.

Section 4.5.4

The Effect of The pH of The Modifying Solution on The Modification of Ni/SiO_2 (I).

In order to examine the effect of the pH of the modifying solutions on nickel leaching and the hydrogenation activity and enantioselectivity of the

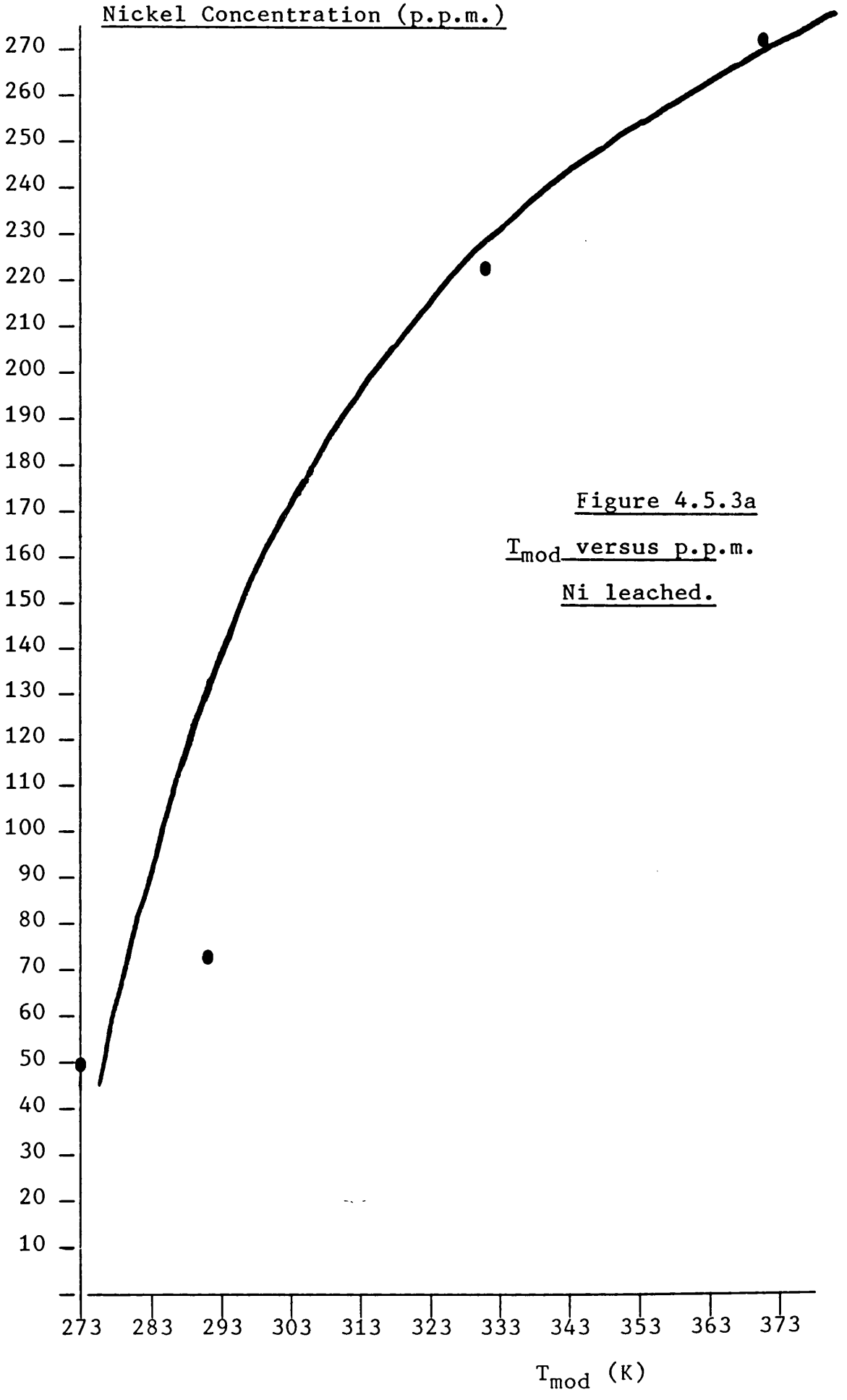


Figure 4.5.3a

T_{mod} versus p.p.m. Ni leached.

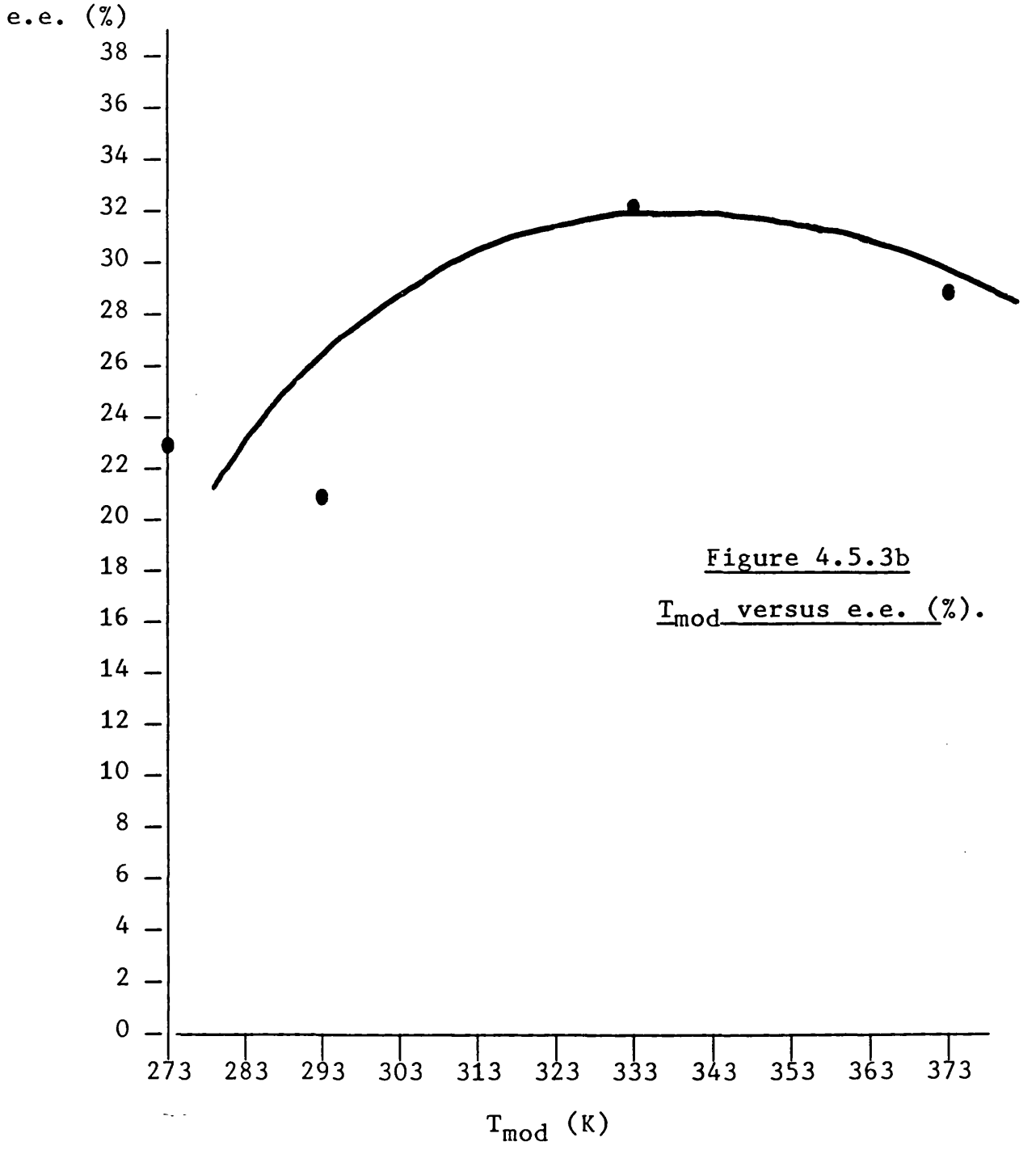


Figure 4.5.3b

T_{mod} versus e.e. (%).

resultant catalyst, different samples of Ni/SiO_2 (I) were modified in T.A./NaBr solutions of pH value in the range 3.2-9.6(i.e from acidic to basic media).

The constants of modification in these reactions were as shown in Table 4.5.4a:-

Table 4.5.4a

[T.A.] mol dm^{-3}	[NaBr] mol dm^{-3}	Volume Of Solution(cm^3)	T_{mod} (K)	t_{mod} hours
6.67×10^{-3}	0.19	100	333	1

The modified catalysts were used in the hydrogenation of MAA (10g) in butan-1-ol (50 cm^3).

Analysis of the product mixtures (by H.P.L.C) from hydrogenation reactions using catalysts modified at pH values higher than 3.2 showed only trace quantities of MAA and MHB. However, Polarimetric measurements of the same product mixtures showed rotation of the plane polarised light i.e. the presence of a chiral species.

The amount of nickel leached and the measured angles of rotation (α^{o}) are given in Table 4.5.4b:-

Table 4.5.4b

Catalyst Ni/SiO_2 (I)	pH	Ni leached p.p.m.	α^{o}
YES	5.1	50	-1.206
YES	7	13	-0.974
YES	9.6	10	-0.236

Section 4.6

The Effect of Nickel Loading - Ni/SiO_2 (II).

To investigate the effect of increasing the metal component on the asymmetric hydrogenation of MAA, a sample of Ni/SiO_2 (II) (% Ni = 30.5) was activated using similar conditions to those established for Ni/SiO_2 (I);

Calcination and Reduction: A sample of the catalyst (1g) was heated to 723 K at 10 K min^{-1} in vacuo and held for 1 hour at this temperature. After cooling, the sample was heated to the same final temperature at the same rate, in a 150 cm^3 min^{-1} flow of hydrogen gas and these conditions maintained for 16 hours.

Modification: The reduced catalyst was modified in a 100 cm^3 aqueous solution with the variables of modification as follows:-

Table 4.6a

$[T.A.]_{mol\ dm^{-3}}$	$[NaBr]_{mol\ dm^{-3}}$	T_{mod} (K)	pH	t_{mod} hours
6.67×10^{-3}	0.19	100	3.2	1

The resultant catalyst was used in the hydrogenation of 10g MAA in 50 cm^3 of butan-1-ol. The nickel leached during modification and the hydrogenation activity and enantiodifferentiating ability of the catalyst is shown in Table 4.6b, as are the results for Ni/SiO_2 (I) activated under the same conditions, for comparative purposes.

Table 4.6b

Catalyst (1g)	Nickel Content (%w/w)	Ni leached p.p.m. / % Ni_{tot} [1]		mole%MHB	e.e.%
Ni/SiO_2 (I)	10.6	220	21	93[a]	32
Ni/SiO_2(II)	30.5	180	6	91[b]	37

1) % Ni_{tot} is the amount of nickel leeched as a % of the metal content of the original catalyst sample.

a) $t_{reaction}$ = 60 hours. b) $t_{reaction}$ = 50 hours.

As the corrosion of Ni/SiO_2 (II), under the same conditions, was less than that of Ni/SiO_2 (I) although enantiomeric excess values were similar, it was decided to investigate the effect of increasing the T.A.

concentration in the modification of Ni/SiO_2 (II).

Section 4.6.1

The Effect of Tartaric Acid Concentration on The Modification of Ni/SiO_2 (II).

Catalyst Ni/SiO_2 (II) was modified using varying concentrations of tartaric acid in the range 6.67×10^{-3} mol dm^{-3} - 6.67×10^{-2} mol dm^{-3}. The other variables of modification were kept constant and were the same as those described in the previous section. The variation in the amount of nickel leached during catalyst modification was plotted with [T.A.] as shown in Figure 4.6.1a.

The hydrogenation activities and enantio-differentiating abilities of these catalysts are summarised in Table 4.6.1a.

Table 4.6.1a

Catalyst Ni/SiO_2 (II) (1g)	[T.A.] mol dm^{-3}	mole%MHB	e.e.%
1	6.67×10^{-3}	91	37
2	2×10^{-2}	89	53
3	3.33×10^{-2}	67	45
4	6.67×10^{-2}	80	39

For 1,2 and 4 $t_{reaction}$ = 50 hours, for 3 $t_{reaction}$ = 70 hours.

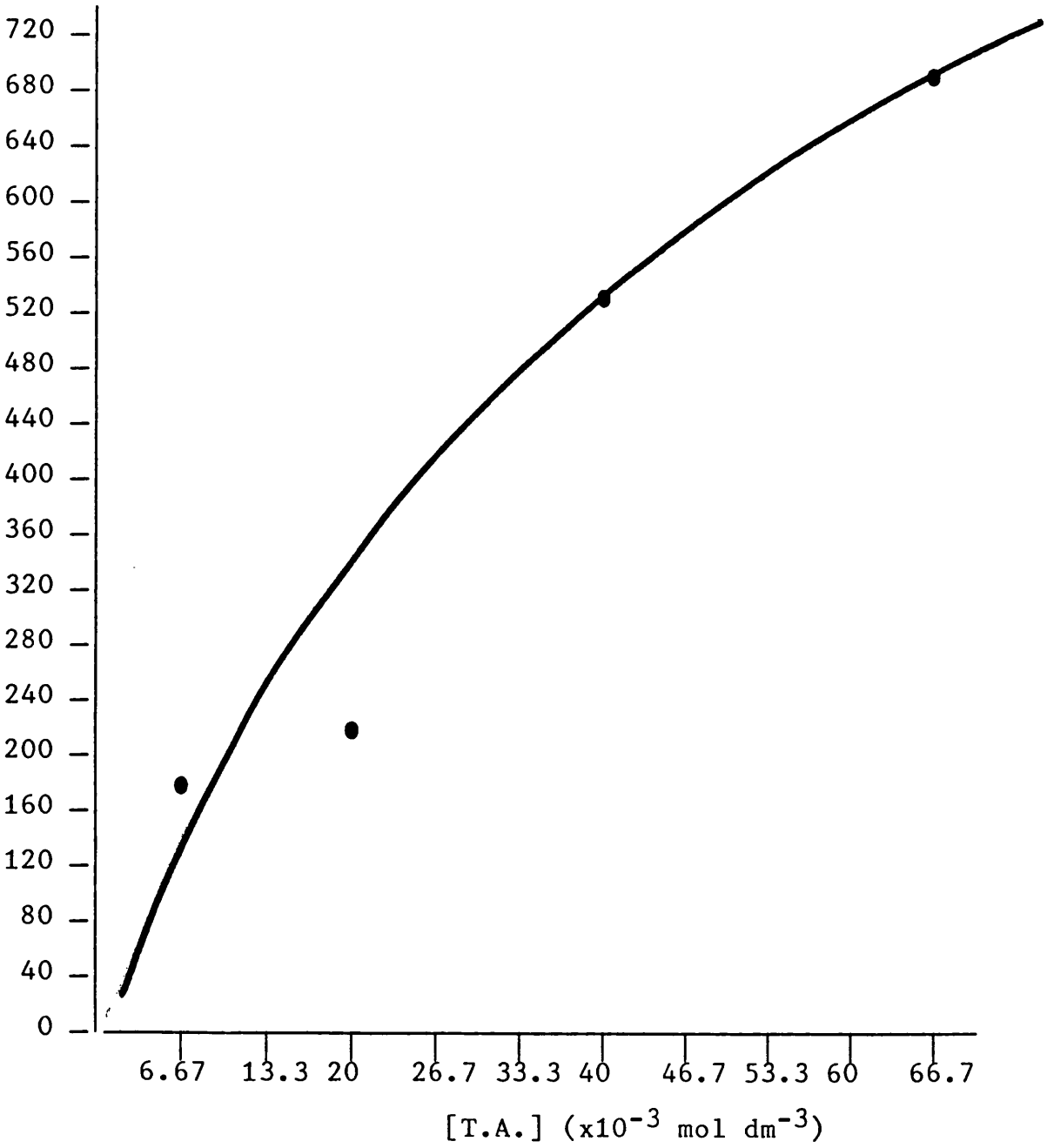


Figure 4.6.1a

[T.A.] versus the nickel concentration of post-modification solutions. (Ni/SiO_2 II).

For entry 3 in Table 4.6.1a, samples were removed during hydrogenation to measure the extent of MAA conversion to MHB; the reaction was then stopped at ca. 70 mole% MHB. This was because previous experiments using a sample of Ni/SiO_2 (II) (1g), that had been modified in a solution of [T.A.] = 3.33×10^{-2} mol dm^{-3}, to hydrogenate MAA, had shown slower rate of conversion and beyond a certain reaction time (and MAA conversion) H.P.L.C. analysis revealed only trace amounts of both product and reactant, [similar to the H.P.L.C. profiles of product mixtures of hydrogenations using Ni/SiO_2 (I) modified at pH values above 3.2].

The re-use of the same sample of Ni/SiO_2 (II) (which exhibited this behaviour of slower MAA hydrogenation, followed by some secondary reaction which drastically reduced the concentration of MAA and MHB) to hydrogenate a fresh sample of MAA, resulted in the same behaviour being observed. This is illustrated in Table 4.6.1b:-

Table 4.6.1b

Catalyst Ni/SiO_2 (II) (1g)	$[T.A.]_3$ mol dm^{-3}	$t_{reaction}$ hours	mole%MHB	α^{o} [1]
YES	3.33×10^{-2}	21	43	-
		80	-	-1.778

1.This is the measured angle of rotation of plane

polarised light of the product mixture, though H.P.L.C analysis revealed only a trace quantity of MHB.

The α^{o} value at 43 mole% MHB is not included in Table 4.6.1b as the samples removed during an on-going reaction were not of a sufficient volume for polarimetric measurements.

Aside from the behaviour of the sample of Ni/SiO_2 (II) modified at the intermediate value of [T.A.] mentioned above, modified Ni/SiO_2 (II) exhibits greater enantiodifferentiating ability than Ni/SiO_2 (I) and is less effected by Ni leaching over the same [T.A.] range e.g. Ni/SiO_2 (I) had no hydrogenation activity when modified in a solution of [T.A.] = 6.67×10^{-2} mol dm^{-3} c.f. Ni/SiO_2 (II) (Table 4.6.1a).

Section 4.6.2.

The Effect of The pH of The Modifying Solution on The Modification of Ni/SiO_2 (II).

The behaviour of Ni/SiO_2 (II) catalysts modified at pH values greater than 3.2 was the same as for Ni/SiO_2 (I) (Section 4.5.4). At pH= 5.1, the amount of Ni leached from a freshly reduced sample of Ni/SiO_2 II was 38 p.p.m. and the measured angle of rotation of the product mixture was -1.660^{o} , though H.P.L.C. analysis showed only trace MAA and MHB in the product mixture.

Section 4.6.3.

The Effect of Nickel Loading - Ni/SiO_2 (III).

A sample of Ni/SiO_2 (III) (1.3% w/w Ni) was activated using the conditions which yielded the optimum e.e. for Ni/SiO_2 (I), but these conditions proved unsuitable for Ni/SiO_2 (III). Post modification, the modifying solution had nickel concentration of 51 p.p.m., which is equivalent to a loss of 40% of the metal content of the catalyst.

In the subsequent use of this catalyst in the hydrogenation of MAA, H.P.L.C. analysis of the product mixture showed no conversion to MHB when $t_{reaction}$ = 30 hours.

Section 4.7

The Effect of The Modification Procedure on The The Initial pH of The Modifying Solution.

The pH of the modifying solution was measured prior to and post-modification of freshly reduced catalyst samples. In most cases, the pH value after the modification step was found to have increased from the pre-adjusted pH value the solution had prior to the modification procedure. The results are summarised in Table 4.7a:-

Table 4.7a

Catalyst* (1g)	[T.A.]$_3$ mol dm^{-3}	Initial pH	Δ pH	mole%MHB	e.e.%
Ni/SiO_2 (I)	6.67×10^{-3}	5.1	+2.9	-	-
Ni/SiO_2 (II)	6.67×10^{-2}	5.1	+2.7	-	-
Ni/SiO_2 (II)	6.67×10^{-2}	3.2	+0.6	80	39
Ni/SiO_2 (II)	3.33×10^{-2}	3.2	+0.6	67	45
Ni/SiO_2 (II)	2×10^{-2}	3.2	+0.3	89	53

* T_{mod} = 333 K t_{mod} = 1 hour

Section 4.8

The Hydrogenation of MAA Over Tartaric Acid/Sodium Bromide Modified Raney Nickel.

By means of comparison, to the behaviour of the Ni/SiO_2 catalysts, a sample of modified Raney Ni was prepared by the method described in Sections 3.1.3 and 3.2.2. During the modification of Raney Ni (t_{mod} =1hour) the vigorous evolution of hydrogen gas was observed.

The freshly prepared sample was used to hydrogenate MAA (10g, 8.62×10^{-2} mol) in butan-1-ol (50 cm^3) under the same conditions used for Ni/SiO_2 catalysts and the resultant catalytic data is summarised in Table 4.8a:-

Table 4.8a

Ni leached	mole % MHB	e.e.%
1680[a] p.p.m.	76	49

$t_{reaction}$ = 50 hours

a Prior to analysis, a substantial amount of a green Ni compound precipitated from the modifying solution. The value stated is the nickel concentration of the solution after precipitation.

Section 4.8.1

Further Studies: Precipitation of The Ni Species From Post-Modification Solutions.

A 'nickel tartrate' type compound was precipitated from modifying solutions by addition of a 60/40% (v/v) butan-1-ol/methanol mixture(100 cm^3). It had been demonstrated previously that the precipitate is active as a heterogeneous catalyst for the reduction of MAA[132].

This was proved to be the case when 0.3g of the precipitate was used in the hydrogenation of MAA (10g) in butan-1-ol (50 cm^3). Figure 4.8.1a shows the presence of MHB in the product mixture as well as MAA and a third peak, which was identified as resulting from the presence of tartrate ion. Figure 4.8.1b illustrates that

Figure 4.8.1a

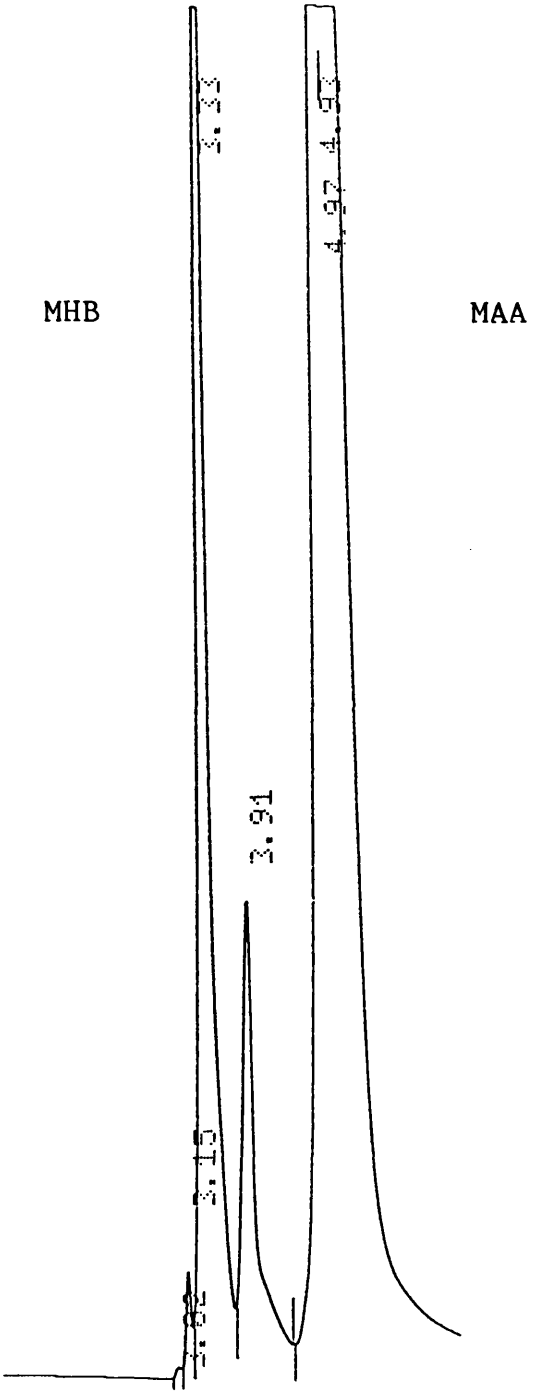
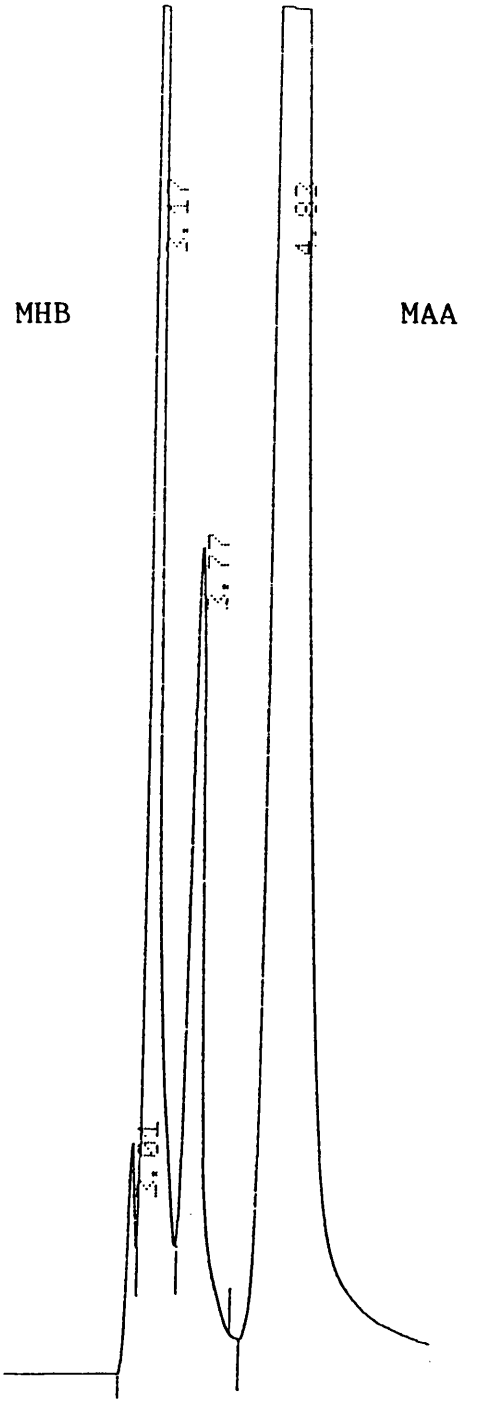


Figure 4.8.1b



The H.P.L. Chromatograms Of The Product Mixtures From Hydrogenation Over The Precipitated Nickel Complex.

as the level of hydrogenation continued to increase, so did the tartrate content of the product mixture.

Polarimetric measurements revealed no rotation of the plane polarised light.

Section 4.8.2

Further Studies: Analysis of Product Mixtures Containing Only Trace Quantaties of MAA And MHB.

In Section 4.5.4, the use of Ni/SiO_2 (I) catalysts modified in solutions of pH value greater than 3.2 was described. A feature of these catalysts was that after the hydrogenation period, H.P.L.C. analysis revealed only trace quantities of the reactant, MAA, and the product, MHB. However, polarimetric analysis showed rotation of plane polarised light- indicative of the presence of a chiral species. In an attempt to discover what was happening to the known reactant and expected product during the course of reaction, H.P.L.C. analysis was carried out on the product; the wavelength of the U.V. detector was varied and the composition of the mobile phase changed. However, no successful resolution of the product mixture has been achieved by this method.

Another analytical method used was Gas Chromatography /Mass Spectroscopy (G.C./M.S.). By comparison with a library of mass spectra, a product of trans-esterification was identified: butyl 3-hydroxy butanoate

The mass spectrum and the library comparison are shown in Figures 4.8.2a.

Section 4.8.3

Further Studies: The Repeated Use of Modified Ni/SiO_2 (II) in The Hydrogenation of MAA.

A sample of Ni/SiO_2 (II) (1g) was activated by the method summarised in Section 4.6 and used in the hydrogenation of MAA to MHB under the same conditions. After the reaction period the product mixture was removed for analysis and the catalyst washed with, and then stored (18 hours) under butan-1-ol. The catalyst was then used in a further hydrogenation of a fresh sample of MAA. The results of each hydrogenation are shown in Table 4.8.3a.

Table 4.8.3a

Catalyst Ni/SiO_2 (II) (1g)	Hydrogenation Reaction	Mole % MHB	e.e.%
YES	1^{st}	92	38
YES	2^{nd}	91	36

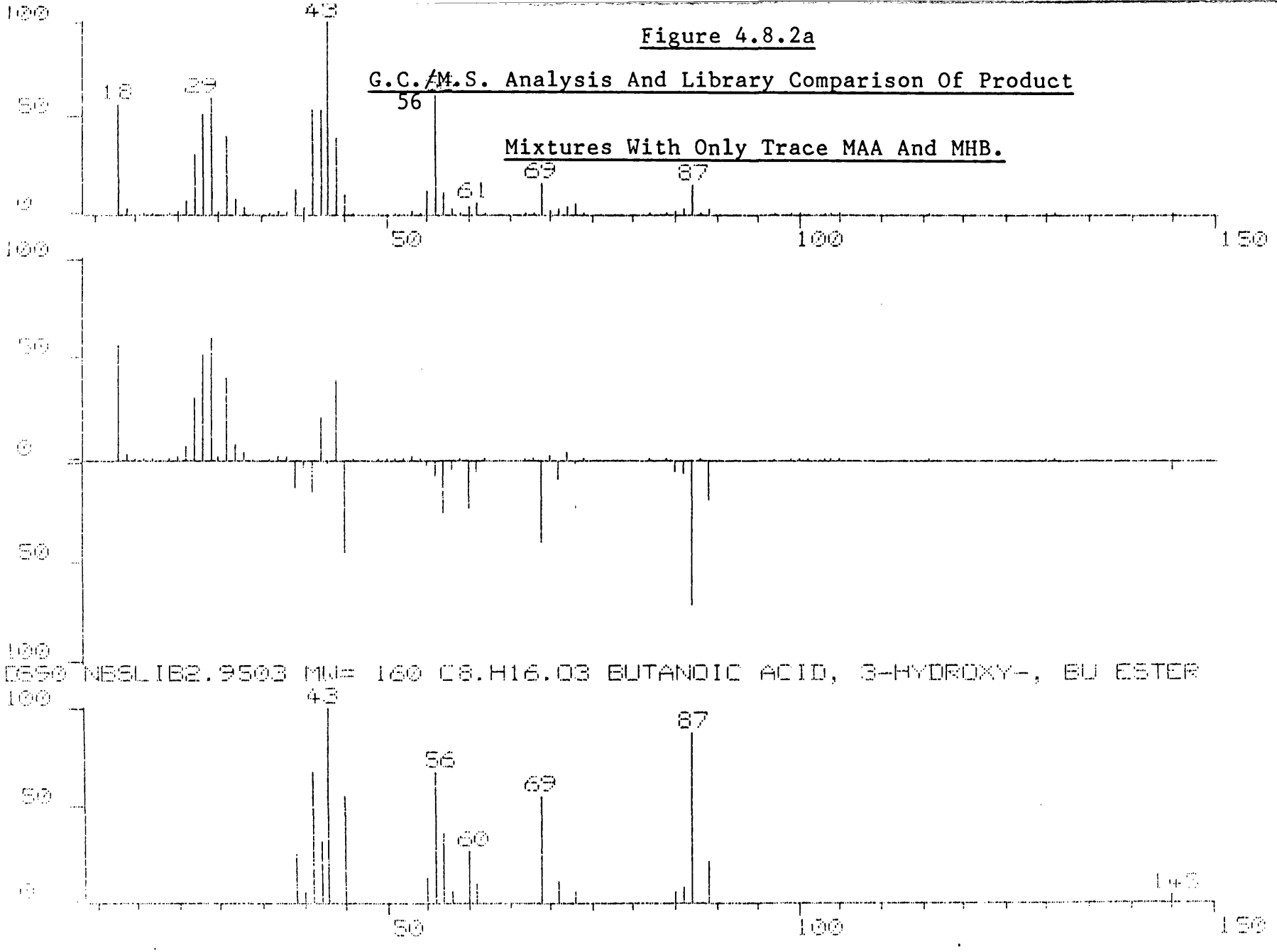
$t_{reaction}$ = 50 hours.

As the results in Table 4.8.3a are within the margin of error of the analysis (Section 3.4.2), it can be

Figure 4.8.2a

G.C./M.S. Analysis And Library Comparison Of Product

Mixtures With Only Trace MAA And MHB.



concluded that there is no loss of activity on using a modified sample of catalyst twice.

Section 4.8.4

Further Studies: The Use of Unmodified Ni/SiO_2 (II) in The Hydrogenation of MAA.

As a comparison to the hydrogenation activity of modified catalysts, a sample of Ni/SiO_2 (II) was reduced and then used in the hydrogenation of MAA (10g) in butan-1-ol. After the reaction period used for modified Ni/SiO_2 (II) ($t_{reaction}$ = 50 hours), analysis of the product mixture from the use of the unmodified catalyst revealed 75% MHB (c.f. 90% from a modified sample). As expected, polarimetric measurements showed no rotation of plane polarised light.

Section 4.9

The Ni/Pt Silica Supported Catalyst.

The Ni/Pt catalyst, prepared by the method described in Section 3.1.1b for the reasons given in Section 4.3.1 (b), proved ineffective as a catalyst for the asymmetric hydrogenation of MAA, when modified under the optimum conditions developed for Ni/SiO_2 (I). As these catalysts were of approximately the same Ni loading (ca. 10%) the presence of platinum in the Ni/Pt catalyst appears to cause a loss of activity. It is worth noting that the nickel leached into the modifying solution from the sample of $Ni/Pt/SiO_2$ was 75% of the total Ni content.

CHAPTER FIVE

DISCUSSION

Section 5 Introduction

In this chapter the enantiodifferentiating ability of nickel catalysts modified in tartaric acid/co-modifier solutions is discussed. In particular, the effects of the catalyst modification and reaction conditions on its use for the asymmetric hydrogenation of methyl acetoacetate, are discussed and comparisons made with explanations given in the literature.

Section 5.1 Catalyst Precursor Preparation And Activation.

The nickel catalysts used in this study were prepared by impregnation of the silica support with aqueous solutions of nickel nitrate (Chapter 3). The nitrate salt was chosen as the source of nickel as it had been demonstrated by Nitta et al.,[47] that catalysts prepared from nickel acetate reduced optical yield, and those from nickel sulphate resulted in a zero optical yield, due to the poisoning effect of residual sulphur. The impregnation method of catalyst precursor preparation was used to enable comparisons to be made with results obtained from other research being carried out in the Glasgow laboratory in to asymmetric catalysis over modified nickel/silica catalysts, in which the catalysts were prepared by a precipitation method[123]. The silica

supported catalyst precursors had an advantage over Raney nickel catalysts in that there was not the same level of impurities, particularly aluminium/alumina, which is known to be detrimental to the enantio-differentiating ability.

For the reduction of the nickel/silica catalyst (1:1) precursor, Nitta[77] reported that the conditions of reduction had only a slight effect on the resultant activity and enantiodifferentiating ability. However, as the catalysts used in this study were of lower metal loading (for example Ni/SiO_2 (I) was 10.6% w/w Ni; Section 3.1.2) it was decided to run temperature programmed reduction experiments to identify the optimum conditions for precursor reduction. This method had proved successful in gauging the optimum conditions for reduction of nickel/silica catalysts used in the hydrogenation of ethene[124]. Unfortunately, the conditions of reduction derived from the hydrogen uptake profile of the T.P.R. experiment proved unsuccessful (Section 4.2) so a literature based determination was adopted. The study which proved the most useful was that by Martin et al.[125], in which it was reported that the pretreatment of nickel/silica catalysts in vacuo and a high flow rate of hydrogen efficiently removed water formed during reduction, the effect being an increased level of reduction and increased average particle

diameter. A high reduction temperature was necessary as it had been shown that nickel is more difficult to reduce when used in conjunction with a support[126].

Satisfied that the conditions of catalyst reduction were sufficient (Section 3.2), the next step was to investigate the second stage of catalyst activation, that is chiral modification, to discover the reason for the lack of success in using similar conditions to those used for Raney nickel for the production of an enantiodifferentiating catalyst (Section 4.2).

Section 5.1.1 The Effect of Ni/SiO_2 Catalyst Modification.

The modifier used throughout this study has been optically pure (R,R)-+-tartaric acid. This compound had been shown to be the best modifier in terms of the enantiodifferentiating ability of a Raney nickel catalyst[98], and has been used in the vast array of studies into heterogeneous nickel catalysts as highlighted in the introduction to this thesis. Also highlighted in the introduction was the effect that the conditions of modification exerted on enantioselective behaviour (for example temperature), as was the non-standard nature of the conditions used by different research groups investigating dissimilar features of the

modified catalyst. An example of the non-standard basis is illustrated by the following example:- Tatsumi[58], studying the conditions of Raney nickel modification by tartaric acid in general, reported optimum values for modification conditions to be:

Modifying solution: 100 cm^3 of a 0.133 mol dm^{-3} aqueous tartaric acid solution.

pH of Modifying solution: 5.0

Temperature of Modification: 273 K

Whereas Izumi[67], reporting the effect of various sodium salt co-modifiers (Section 1.4.4), for this same set of conditions used the following values:

Modifying solution: 100 cm^3 of a 0.067 mol dm^{-3} aqueous tartaric acid solution.

pH of Modifying solution: 3.2

Temperature of Modification: 373 K

An earlier attempt to provide a set of standard conditions for the modification of Raney nickel catalysts that optimised enantiodifferentiating ability was the subject of the Ph.D. thesis of Christie[22]. This approach, coupled with similar study of substrate (MAA) reaction conditions, proved to be successful, leading to the achievable enantiomeric excess rising to 85% (at 100% conversion). Thus, the modifi cation procedure developed by Christie (Section 3.2.2) was used as

the standard in the initial stage of this research, that is, the modification step of catalyst activation.

However, initial experiments with the nickel/silica catalysts modified under these conditions resulted in catalysts with zero hydrogenation activity and enantio-differentiating ability. The large quantity of published material on successful studies of tartaric acid modified nickel catalysts suggested that the reason for poor enantioselectivity did not lie with the choice of the modifying reagent, tartaric acid, for the modification step of catalyst activation. It was therefore decided that the poor catalyst performance was the result of the modification procedure developed for Raney nickel. This idea was strengthened by the observation that the catalyst turned from black (prior to modification) to to grey/green (post-modification), whilst the modifying modifying solution was green in colour (Section4.2). These features were taken as indicative of the corrosion of nickel metal to nickel (II) ions by the modifying solution. The control experiments described in Section 4.5.1, where a calcined sample of Ni/SiO_2 (I) was modified by a similar method to that used for reduced catalysts and a reduced sample of Ni/SiO_2 (I) was modified by treatment in a solution of HCl (pH=3.2), showed that, in each case, the extent of catalyst corrosion was only a fraction of that found in tartaric

acid modification of reduced Ni/SiO_2 (I) under similar conditions. Hence the nickel (II) ions found in the post modification solution were not the result of a low extent of catalyst reduction or simply due to the acidity of the modifying solution. The results of this initial study of the modification procedure showed that the effect of the variables of modification should be considered in terms of nickel corrosion as well as the enantiomeric excesses produced by the resultant catalysts in the asymmetric hydrogenation of MAA. While the idea of catalyst corrosion is not new[94], no attempts to quantify this effect have been made previously.

Considering the effect of tartaric acid concentration, the results of the present study show that the Ni/SiO_2 catalysts used are more sensitive to variations in the concentration of tartaric acid than would appear to be the case from other reports[58,98]. Figure 4.5.1a illustrates that increasing the concentration of tartaric acid in the modifying solution (for a sample of Ni/SiO_2 (I)) results in an increase the amount of nickel (II) in solution. However, although catalyst corrosion increases with [T.A.], the enantio-differentiating ability of Ni/SiO_2 (I) reaches a maximum (e.e.= 29%) for modification in a 6.67×10^{-3} mol dm^{-3}

solution of tartaric acid and then declines. Thus an initial increase in the extent of catalyst corrosion enhances the enantioselectivity, but at higher levels of corrosion the catalyst has no hydrogenation activity, and consequently no enantiodifferentiating ability. It is worth noting that the optimum of tartaric acid concentration for the modification of Ni/SiO_2 (I) is about 1/10 of the value normally used in other studies. The effect of increasing tartaric acid concentration on Ni/SiO_2 (II) is illustrated in Figure 4.6.1a. Again, nickel corrosion increases with tartaric acid concentration whilst the enantiodifferentiating ability also passes through a maximum (e.e.=53%, [T.A.]=2 x 10^{-2} mol dm^{-3}, Table 4.6.1a) when the tartaric acid concentration is approximately 1/3 of that typically used for the modification of Raney nickel (for example[22] [T.A.]=6.7 x 10^{-2} mol dm^{-3}) although some asymmetric activity remains when Ni/SiO_2 (II) is modified in a solution where the tartaric acid concentration is 6.67 x10^{-2} mol dm^{-3}, unlike Ni/SiO_2 (I). The complicated behaviour of the Ni/SiO_2 (II) sample modified in a solution of tartaric acid concentration 3.33 x10^{-2} mol dm^{-3}, is more difficult to explain. The modification procedure is obviously reducing the overall hydrogenation activity of the sample, as the time taken to reach 67 mole % MHB was 70 hours compared to 50 hours

to reach 90% for the samples modified at other tartaric acid concentrations.

Comparing the behaviour of Ni/SiO_2 (I) and Ni/SiO_2 (II), modified under the same conditions, the catalyst with the higher metal load, Ni/SiO_2 (II) (30.5% w/w Ni compared to 10.6 %) proved to be more resistant to corrosion (Table 4.6a). The extent of corrosion of each catalyst can be considered in terms of the amount of nickel lost during modification relative to the amount of nickel initially present; Ni/SiO_2 (II) lost 6% compared with the 21% lost by Ni/SiO_2 (I). In order to determine if this corrosion was perhaps more of a feature of low metal loaded catalysts, it was decided to prepare and modify a sample of Raney nickel according to the method described by Christie[22]. The modification step proved to be very corrosive (Section 4.8), a nickel complex precipitating from the solution on standing and the remaining solution containing 1680 p.p.m. Ni. Whilst this feature of the modification had not been determined by Christie, the present results, when coupled with the report by Sachtler et al.,[94] of nickel leaching during modification, it can be concluded that nickel corrosion is a constant feature of the modification step, although it has been relatively ignored in previous interpretations of asymmetric catalytic activity.

The lack of success in producing asymmetric activity

in a modified sample of Ni/SiO_2 (III) may be ascribed to the use of too high a value of tartaric acid concentration for the low metal loading of this catalyst (1.3% w/w Ni). The experience of using a lower tartaric acid concentration for Ni/SiO_2 (I) than Ni/SiO_2 (II) for optimising enantiodifferentiating ability would suggest the use of an even lower value of tartaric acid concentration for Ni/SiO_2 (III). However the decline in achievable enantiomeric excesses with decreasing metal loading, rendered the determination of an optimum tartaric acid concentration for Ni/SiO_2 (III) unnecessary.

In summary, the tartaric acid concentration used has a marked effect on the leaching of nickel metal from the catalyst, which is more pronounced for catalysts of lower metal loadings. The fact that the greatest enantiodifferentiating ability is observed when the level of catalyst corrosion is neither at a minimum or maximum suggests that this process is an important feature of the modification procedure which requires regulation.

In contrast to the findings of this study, the report by Tatsumi[58], stated that the enantiodifferentiating ability of Raney nickel catalysts was unaffected by increasing the concentration of tartaric acid from 2.67 x 10-2 to 0.67 mol dm^{-3}, and many subsequent studies

have used concentrations within this range. For example, concentrations of 6.67×10^{-2} mol dm^{-3} [22,98] (the concentration used initially in this study) to 0.13 mol dm^{-3} [67] have been used for Raney Ni modification and an intermediate value of 0.11 mol dm^{-3} used by Nitta[77] in the modification of a Ni:SiO_2 (1:1) catalyst. However, in general, no comment on the concentration of modifier used or on its effect was made. An exception is found in a report by Sachtler et al.,[94] in which a decline in the metal loading is commented on but, as the tartaric acid concentration was constant in each of their various modification procedures, they linked the observed catalyst corrosion to the overall modification procedure and not directly to tartaric acid concentration.

The next variable of modification considered in this study was the initial pH of the solution. Throughout the course of this study, the desired asymmetric activity has only been found for catalysts modified in solutions of pH = 3.2. In contrast, the pH of modification most commonly used in the reported literature has been 5.1 (the isoelectric point of tartaric acid), this value being reported to give optimum enantioselectivity[98]. Tatsumi[58] related the pH of modification to the amount of adsorbed tartaric acid, and found this to decline with increasing pH which he explained as the result of

the formation of sodium tartrate which desorbed from the Raney nickel surface. However, this idea of unsatisfactory surface coverage of adsorbed tartaric acid at higher pH values (and hence lower enantio-differentiating ability in the catalysts) is countered by the findings of Klabunovskii[64], who achieved maxima in the optical yield at both low (pH=2) and high (pH=13) pH values. The pH value used determines the form of tartaric acid exposed to the catalyst though; the forms at low, intermediate and high pH values being $HO_2CCH(OH)CH(OH)CO_2H$, $^-O_2CCH(OH)CH(OH)CO_2H$ and $^-O_2CCH(OH)CH(OH)CO_2^-$ respectively. Clearly the choice of pH of solution influences the form of tartaric acid that would be adsorbed on the nickel surface.

Regardless of the form of tartaric acid which is present at the pre-adjusted pH prior to modification, considerable changes occur in the solution during the modification process. These include a progressive build-up of nickel complex in the solution due to the corrosion of the catalyst and, as shown in Table 4.7a, a progressive increase in the pH of the solution during the modification process, which may be as much as 2.9 pH units.

Wittmann et al.[127] also reported changes in pH during modification and claimed that these could be overcome by the continued addition of tartaric acid and that, in

consequence, the reproducibility of the results was improved. However, in the present study, the results suggest that any beneficial effects of keeping pH constant in this way, in terms of the enantio-differentiating ability of the resultant catalyst, would be negated by increasing the concentration of tartaric acid.

The results presented in Sections 4.5.4 & 4.6.2 show the effects of using initial pH values higher than 3.2 for Ni/SiO_2 (I) & Ni/SiO_2 (II) respectively. The extent of nickel leaching during modification declines with increasing pH, though significant as shown in, for example, the report by Sachtler et al.,[94] where pH of modification was 5.0. However, when the Ni/SiO_2 catalysts were modified in solutions of pH value greater than 3.2, namely 5.1, 7.0 and 9.6 and then to hydrogenate samples of MAA, a surprising effect was observed in that H.P.L.C. analysis revealed only trace quantities of either the reactant (MAA) or the desired product (MHB) after the reaction period. Further H.P.L.C. analysis proved unsuccessful in determining the nature of the reaction product although the product mixture rotated plane polarised light, indicating that some asymmetric reaction had occurred. G.C.M.S. analysis identified the presence of butyl hydroxybutanoate, a product of trans-esterification. This process had been reported to occur

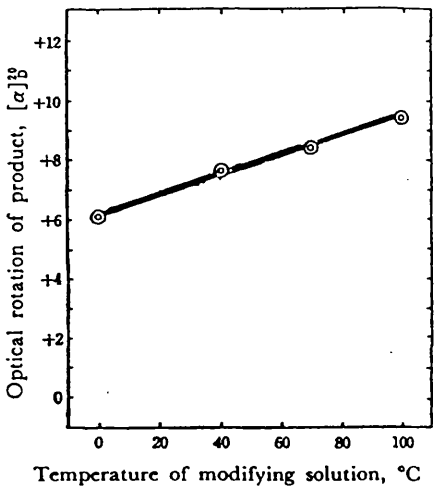
in the asymmetric hydrogenation of MAA over nickel powder catalysts but only when the temperature of reaction exceeded 373 K[42], which is 30 K above the reaction temperature used in this study, but has not been previously reported for the conditions used in the present study. Further study into the hydrogenation behaviour of Ni/SiO_2 (I) & Ni/SiO_2 (II) modified at pH values > 3.2 is required, observing the outcome at lower levels of MAA conversion, as was the practise of Harada et al.,[60] who stopped reactions at 40% conversion to measure optical yield.

In conclusion, a pH value of 3.2 for the modifying solution was the only value that resulted in the desired asymmetric activity being found in the catalysts used in this study.

The next variable of modification to be considered in this study was the temperature of modification; the findings of which are discussed after a consideration of the literature reported effect of this variable. The temperature of modification has been extensively studied for various modifying reagents, and for tartaric acid it has been demonstrated that increasing the temperature increased the enantioselectivity of the resultant catalyst[58,68,98] (Figure 5.1.1b).

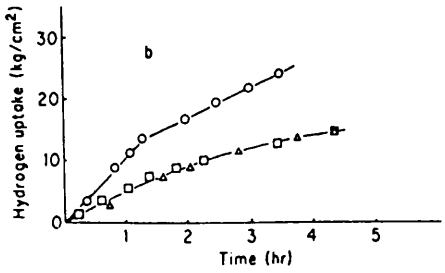
Figure 5.1.1b

The Effect of The Temperature of Modification.



Tatsumi[58] explained the increase in enantioselectivity in terms of an intensified interaction of the tartaric acid with the nickel metal with elevation of modification temperature; the result of which is the modifying reagent spreads itself over the surface of the catalyst, leading to a catalyst with many compactly adsorbed asymmetric centres. As a consequence of this, Tatsumi considered that the overall catalytic hydrogenation activity would decrease upon modification. However, in a study by Tanabe[59], the hydrogenation activity of Raney nickel was shown to be unchanged by modification when glutamic acid was used as the modifying reagent, whereas it increased when tartaric acid was used (Figure 5.1.1c). The increased hydrogenation activity of tartaric acid modified nickel/silica catalysts has also been demonstrated in the present study (Section 4.8.4).

Figure 5.1.1c



Rates of hydrogenation of MAA; Modifying Reagent
(□) none
(△) glutamic acid
(○) tartaric acid

In Section 4.5.4 of this study, the effect of increasing the temperature of modification was shown to be an increase in the amount of nickel corroded from the catalyst. For Ni/SiO_2 (I) the amount of nickel lost to the solution increased linearly in the temperature range 273-373 K (Figure 4.5.3a), though the enantioselectivity increased from 273K to 333K and then declined (Figure 4.5.3b), in contrast to the findings of Tatsumi (Figure 5.1.1b). Similar to the findings for the effect of varying the tartaric acid concentration, these results obtained by varying the temperature of modification indicate that, to some extent, the corrosive formation of a complex is beneficial to the resultant enantio-differentiating properties of a catalyst. However, beyond a certain point corrosion becomes detrimental to the overall activity and enantioselectivity of the catalyst.

The length of the modification step in this study was held constant at 1 hour, consistent with the majority of work on tartaric acid modified nickel catalysts[22,98]. In view of the evidence of the corrosive nature of modification in this study, it is unlikely that the model for the generation of an asymmetric catalyst by the quick, simple adsorption of tartaric acid (length of modification = 10 minutes) proposed by Tatsumi[58] is correct; in the present study, visual examination showed

that the green coloration of the modifying solution progressively increased over 1 hour, although no attempt was made to quantify this effect.

Section 5.1.2 The Effect of NaBr as The Co-Modifier.

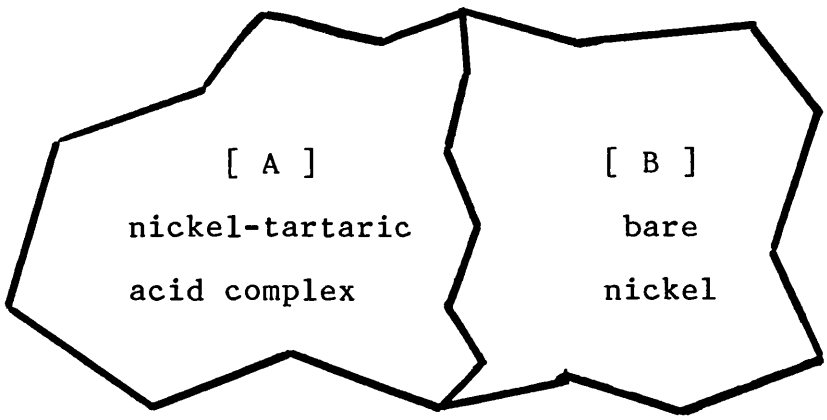
As noted in Section 1.4.4, several reports are extant in the literature which show beneficial effects of the inclusion of sodium bromide in the modifying solution in increasing the enantioselectivity of the modified catalyst. There is, however, considerable debate as to the precise mode of action of sodium bromide. In the model proposed by Izumi and co-workers (Section 1.5.1), the use of sodium bromide was as a poison; they considered the Raney nickel to preferentially adsorb tartaric acid on one part of the catalyst while the sodium bromide was adsorbed on another part, poisoning this surface area which they considered was responsible for racemic hydrogenation. On the other hand, a quite different mode of action has been suggested by Sachtler and co-workers (Section 1.5.1), who considered that the presence of sodium bromide resulted in a shift in the equilibrium position, as defined by the solubility product, of the sparingly soluble nickel complex, responsible for enantiodifferentiating ability, causing less of it to be washed into the modifying solution.

The results obtained in the present study (Section 4.5.2) show that whilst the presence of sodium bromide had little effect on the amount of nickel leached during the modification of Ni/SiO_2 (I), it nevertheless caused a slight decrease in the extent of conversion of MAA to MHB and an increase in the achievable enantiomeric excesses, indicative of the poisoning of non-selective sites. It may be concluded that the nature of these sites cannot be that described by Izumi[92], as the catalysts used in this study contained no aluminium. Equally, the explanation given by Sachtler[108] for the mode of action of sodium bromide in increasing enantioselectivity cannot be true in this case, as the nickel content of the post-modification solution was virtually the same, irrespective of whether or not sodium bromide was present in the modifying solution.

In another study in our laboratory[133] it has been shown that whilst the nickel (II) tartrate complex, which is formed in the modifying solution, is indeed active for the enantioselective hydrogenation of MAA, its activity and enantioselectivity are sufficiently different from those of the modifed catalyst to indicate that this complex is not the seat of enantio-differentiation in the modified catalyst itself. Further, the washing treatment of the catalyst after modification will ensure that the removal of any

nickel (II) tartrate remaining on the catalyst surface is complete before the latter is used for reaction.

Taking all these various factors into account, it is proposed that the modification process results in the formation of a surface nickel-tartaric acid complex, which is strongly bound to the catalyst and which, in contrast to the conclusions of Sachtler et al., is not simply nickel (II) tartrate. It is also proposed that this surface "tartaric acid" complex acts as the site for enantioselective hydrogenation. Accordingly, the catalyst surface may be represented as:-



with "complexed" and "bare" nickel sites co-existing on the surface; enantioselective hydrogenation of MAA occuring on sites [A] and racemic hydrogenation of MAA occuring on sites [B]. Within this model the effects of sodium bromide are most readily interpreted in terms of a partial poisoning of the "bare" nickel sites [B]

with a resultant decrease in the extent of racemic hydrogenation.

Section 5.1.3 The Effect of The Metal Loading of Nickel/Silica Catalysts.

The nickel/silica catalysts used in this study increased in metal loading in the order:-

	Ni/SiO_2 (III)	<	Ni/SiO_2 (I)	<	Ni/SiO_2 (II)
% w/w Ni	1.3		10.6		30.5

The catalyst with the highest metal loading [Ni/SiO_2 (II)], when modified, gave the greatest enantiomeric excesses when used the asymmetric hydrogenation of MAA. In the comparative study of reduced samples of Ni/SiO_2 (I) & Ni/SiO_2 (II), modified under the same conditions, it was demonstrated that the higher metal loaded catalyst was less affected by the corrosive nature of the modification process; the nickel leached from Ni/SiO_2 (II) = 180 p.p.m. Ni, compared to 220 p.p.m. Ni leached from Ni/SiO_2 (I).

An explanation as to why catalysts of higher nickel loading exhibited higher enantiodifferentiating ability was offered by Nitta et al.[47] They considered that a necessary feature of the unmodified catalyst was that it should have a large and narrow crystallite size distribution, as described in Section 1.4.4. As it had

been demonstrated that catalyst precursors with high metal loading give catalysts with large crystallite size in comparison to low loaded metal precursors[128], Nitta et al. concluded that for nickel catalysts large metal crystallites allow regular adsorption of tartaric acid and enhance enantioselectivity, while smaller crystallites remain unmodified and are responsible for racemic hydrogenation. A flaw in this model for the effect of increasing metal loading is that it ignores the corrosive nature of modification. Indeed, it has been demonstrated by Keane and Webb[134] that small nickel particles, of highest free energy, are preferentially corroded during catalyst modification.

In view of the results of the present study, it is considered that the effect of using nickel/silica catalysts of higher nickel loading is to produce catalysts of higher crystallite size that are more resistant to the corrosiveness of modification.

Section 5.1.4 The Effect of The Addition of Platinum to a Ni/SiO_2 Catalyst Precursor.

During initial work a catalyst precursor that contained 0.1% w/w platinum, 10% w/w nickel / silica catalyst was prepared by the impregnation method (Section 3.1.1b), the platinum being added in an attempt

increase the extent of nickel reduction (Section 4.3.1) as this was thought to be the cause of inital poor results.

The addition of trace quantities of platinum to a nickel/kieselguhr catalyst had previously been demonstrated to increase the enantiodifferentiating ability with respect to a monometallic nickel/kieselguhr catalyst[114]. Similarly, Nitta[117] reported a beneficial effect on the enantioselectivity of a nickel/silica catalyst by incorporation of trace quantities of palladium, although this was limited to the boundaries of the catalyst precursor reduction conditions, Pd addition enhancing the enantioselectivity of catalysts reduced under mild conditions, but greater enantioselectivity being achieved with monometallic nickel/silica catalysts when reduction conditions were optimised.

In this study the inclusion of a platinum component failed to produce a successful asymmetric catalyst, even when reduced under the conditions used for Ni/SiO_2 (I), a catalyst of approximately the same nickel loading as the nickel/platinum silica catalyst (ca. 10%). Indeed, the presence of platinum resulted in a catalyst which was totally inactive for the hydrogenation of MAA (Section 4.9). Whilst at first sight this is surprising, the detrimental effect of platinum may be explained by

considering the corrosive nature of the modification step. As nickel metal has been shown to be corroded during modification, the presence of the more noble platinum metal would accelerate this process, since in this system it may act as a local cathode[129], and result in almost total leaching of nickel [75% Ni leached from the nickel/platinum/silica catalyst compared to 21% from Ni/SiO_2 (I)].

Section 5.2.1 The Effect of The MAA Hydrogenation Conditions.

The major objective of this study into the asymmetric hydrogenation of MAA over tartaric acid modified nickel/silica catalysts was concerned with the activation process including both catalyst reduction and modification. The basis of the hydrogenation conditions used were derived from the work on Raney nickel carried out at this laboratory by Christie[22], but with some modifications, made in the light of literature reports of the effects of hydrogenation reaction variables on achievable enantiomeric excesses (Section 1.4.5).

The first necessity of this study was to develop a suitable system for use in all stages of catalyst activation and MAA hydrogenation as that used by Christie was considered unsuitable for the preparation and handling of nickel/silica catalysts. The development

of the reactors used and the hydrogenation procedure that proved most successful are described in Section 3.3.1 to Section 3.3.6. In summary, reproducible results in the hydrogenation of MAA were achieved using catalytic Reactor II, which allowed constant agitation of the substrate/catalyst suspension with the bubbling of hydrogen gas directly into it. This system reduces diffusion limitations[48] inherent in the static hydrogenation system used initially and which has been shown to be detrimental to the optical yield in the asymmetric reduction of EAA by Klabunovskii[73].

The temperature of reaction used throughout this study was 343 K. This hydrogenation variable has been shown to effect the achievable optical yield in several studies[60,62]. Klabunovskii[70] reported that while catalytic activity should increase with temperature, for stereoselective (and enzymatic) catalysis the increase in rate is only observed over a narrow temperature band, and he found this to be the case for EAA hydrogenation over tartaric acid modified Raney nickel. The reason why temperature should have this effect was explained by Klabunovskii[70] in terms of thermal inactivation of the enantioselective centres on the catalyst surface at higher temperature.

As temperature of reaction was not studied in the

course of the work of this thesis, 343 K may be in the beneficial (to enantiodifferentiating ability) narrow temperature range, though not the exact optimum value. This could be one reason why enantiomeric excess values (ca. 50%) recorded during this study have not reached the level of others[65] (90%).

Although the early studies of asymmetric catalysis used hydrogen pressures of 80 atmospheres[38], later studies by Klabunovskii[73] and Nitta[75] indicated that the highest optical yields were achievable in reactions at 1 atmosphere pressure of hydrogen. In contrast, Christie[22] reported very low enantiomeric excesses in atmospheric pressure hydrogenations of MAA, with a dramatic improvement in asymmetric activty when the reaction was carried out in an autoclave (hydrogen pressure = 90 atmospheres).

As Nitta ascribed the better performance of his modified catalyst at lower pressure to the high activity of the nickel/silica catalyst (compared to Raney Ni), this study initially concentrated on static 1 atmosphere hydrogenation reactions. The static reaction approach was later dropped in favour of the method described at the start of this section, reducing diffusion limitations and increasing reproducibility.

In their attempts to analyse their findings, Nitta[75]

concluded that reaction orders on the modified and unmodified sites are different from each other, while Christie[22] concluded that the selective process which occurred on the catalyst surface was dependent on surface hydrogen concentration. It is believed that the hydrogenation method used in this study, of sparging the catalyst/reaction mixture with hydrogen, would ensure high concentration of hydrogen at the catalyst surface, giving a similar reaction situation to the high pressure studies by Christie.

The solvent used throughout the course of this study has been butan-1-ol. Klabunovskii[73] studied the effect of varying solvent and concluded that the highest enantiomeric excesses were to be achieved with solvents of high dielectric constant, particularly anhydrous alcohols. Consideration of the reaction temperature used though favours the use of butan-1-ol over the lower boiling methanol, ethanol and propanol. Klabunovskii[70] interpretated the dependence of asymmetric yield on solvent polarity to be indicative of an ionic transition state in the asymmetric hydrogenation of the substrate. The detrimental effect of water (the exception to his described relationship between dielectric constant and asymmetric yield) he reasoned was the result of its disruption of the surface complex which controlled enantioselectivity.

Section 5.3 The Mechanism of The Enantioselective Hydrogenation of MAA.

From the results gained in the present study of the modification procedure, a mechanism for the enantioselective hydrogenation of MAA over tartaric acid modified nickel catalysts can be proposed. The modification process produces a nickel tartrate surface complex that is responsible for enantiodifferentiation, but can also be removed from the catalyst surface and washed into solution as nickel (II) tartrate. The variables of modification (for example tartaric acid concentration), traditionally linked to the asymmetric activity of the resultant catalyst[98] have been directly linked to the extent of formation (by corrosion of nickel metal) of a soluble nickel (II) tartrate complex as well (Chapter 4), presumed to be the result of the decomposition of the surface nickel tartrate species. As the variables of modification have been proven to affect the amount of corroded nickel (II) tartrate, it can be assumed that they also affect the amount of surface nickel tartrate complex and thus the enantiodifferentiating ability of the resultant catalyst. It is worth noting that the modification procedure can be too severe and remove all hydrogenating activity from Ni/SiO_2 catalysts (Section 4.3.2).

The mechanism of enantiodifferentiation is therefore considered to be caused by hydrogen bonding from the surface nickel tartrate complex controlling the adsorbed face of the substrate, MAA. The fact that all hydrogenating activity is lost by catalysts that have suffered an excess of nickel corrosion suggests that there is a requirement for nickel metal as well as the nickel tartrate complex in the system. It is probable that the enantioselective hydrogenation of MAA proceeds by hydrogen spill-over from nickel metal to the surface nickel tartrate/MAA complex by the method described in Mechanism III (Section 1.5.1).

Due to the continual adsorption of tartaric acid and surface nickel tartrate complex formation followed by washing of nickel (II) tartrate, at the end of the modification step unmodified nickel remains, which is responsible for the racemic hydrogenation of MAA, and which is partially poisoned by sodium bromide as discussed in Section 5.1.1.

The nature of the nickel (II) tartrate complex recovered from modifying solutions is uncertain, especially as the nickel tartrate complex used in some experiments by Hoek and Sachtler[68] had no hydrogenating ability. The complex recovered in this study did have hydrogenating activity though it exhibited little or no enantiodifferentiating activity (Section 4.8) in the

limited test carried out using it. The appearance of a third peak during H.P.L.C. analysis, identified as tartaric acid, confirmed that the nickel precipitate was a nickel tartrate type complex though. A more detailed study of the precipitate from modifying solutions and of nickel (II) tartrate as catalysts for the enantio-selective hydrogenation of MAA has been reported by Keane and Webb[133], who found enantioselective behaviour with these compounds, though not as great as with their Ni/SiO_2 catalysts.

Section 5.4 Concluding Remarks.

The work described in this thesis has shown that the enantioselective ability of tartaric acid modified nickel/silica catalysts is determined by the extent of nickel complex formation/corrosion during the modification step. The nature of corrosion/modification implies that there can be no defined optimum set of values for the modification variables applicable to all nickel catalysts; rather the variables of modification should be set with regard to the particular catalyst. Also, higher metal loaded catalysts are more resistant to corrosion than lower loaded catalysts and higher enantiomeric excesses are achievable. In addition, a mechanism has been proposed for enantioselective hydrogenation which also explains racemic hydrogenation.

A more exact picture of the mechanism could be gained if in further work the nature of the nickel complex was identified by, for example, spectroscopic methods.

Possible methods of increasing the enantiodifferentiating ability of nickel/silica catalysts include a more gradual modification procedure- addition of the tartaric acid to be used in the modification in sequential steps would possibly enhance adsorption of the nickel complex, as further corrosive chemisorption of tartaric acid would be limited. Further work in which the variables of hydrogenation not examined during this study are determined may also provide a means of improving the asymmetric hydrogenation activity of nickel/silica catalysts, for example, the use of lower boiling alcohols (methanol, ethanol) which were demonstrated to improve catalyst enantiodifferentiation by Klabunovskii[73] may be studied, although this would also necessitate a study of reaction temperature. It would also be interesting to study the use of hydrogen pressures greater than atmospheric pressure in MAA hydrogenation reactions to observe if the vast improvement in enantiodifferentiating ability found for Raney nickel catalysts by Christie[22] was mirrored for nickel/silica catalysts.

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